federal register

Friday
April 6, 1979

Part V

Department of Health, Education, and Welfare

Food and Drug Administration

Phenformin Hydrochloride

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

Phenformin Hydrochloride; Denial of Petition for Reconsideration

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency is publishing the Commissioner's Denial of Petition for Reconsideration of his final decision withdrawing approval of new drug applications (NDA's) for phenformin hydrochloride.

ADDRESS: The Denial of Reconsideration may be seen in the office of the Hearing Clerk (HFA–305), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Richard A. Anderson, Office of the Associate Commissioner for Health Affairs (HFY–21), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1170.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the **Federal Register**, the agency is publishing the Commissioner's Final Decision and the Administrative Law Judge's Initial Decision on the withdrawal of approval of NDA's for phenformin hydrochloride. The Commissioner's Denial of Reconsideration is set forth below:

Denial of Petition for Reconsideration

On November 15, 1978, I issued a final decision, following a formal evidentiary public hearing, withdrawing approval of the new drug applications (NDA's) for phenformin hydrochloride. The decision was based on a determination that phenformin is not shown to be safe for use under the conditions of use on the basis of which the NDA's were approved. A notice of the avilability of the decision was published in the **Federal Register** of November 24, 1978 (43 FR 54995).

On December 22, 1978, the Committee for the Care of the Diabetic (CCD), a non-party participant in the withdrawal preceeding, submitted a petition for reconsideration of the final decision, as provided by 21 CFR 12.139. Such a petition must demonstrate that relevant data information, or views contained in the administrative record were not previously or adequately considered, that the petitioner's position is not frivolous and is being pursued in good faith, that the pettitoner has demonstrated sound public policy grounds supporting reconsideration, and that reconsideration is not outweighted by public health considerations or other public health interests. 21 CFR 10.33(d). A petition will be considered only if it is submitted within 30 days of the date of the decision involved, if submitted late, the petition "shall be denied as untimely." 21 CFR 10.33(g).

According to CCD reconsideration of the phenformin decision is necessary to allow CCD to present "new facts." The new facts identified by CCD consist of the report of an audit conducted by FDA into alleged errors and discrepancies in data of the University Group Diabetes Program (UGDP). The UGDP study concluded that there was increased cardiovascular mortality among patients taking the oral hypoglycemic drugs, one of which was phenformin.

The FDA auditors reviewed the records of 129 patients who had died in the course of treatment under the study, plus those of 21 surviving patients.[1] The purpose of the audit was to assess whether the scientific paper published by the UGDP accurately reflects the data which the UGDP coordinating center received from the physicians participating in the study and whether any discrepancies found by the auditors affect the conclusions of the study. The auditors compared case report forms from individual clinical investigators with the data stored in the computer file and with the summary tables published in the UGDP's reports. The availability of the audit report and its findings was first announced by FDA on November 6, 1978. Further notice of its availability was published in the **Federal Register** of November 14, 1978 (43 FR 52732).

The audit concluded that "while there are certain errors and discrepancies between the data file of the UGDP study and the published reports, none of these appears to be of sufficient frequency or magnitude to invalidate the finding that cardiovascular mortality was higher in the groups of patients treated with tolbutamide plus diet and phenformin plus diet compared to the groups treated with placebo or insulin."

CCD argues that, because the audit report is now available for review, a reconsideration of the decision to withdraw approval of the phenformin NDA's is required.

One answer to this assertion is that I did not rely on the UGDP study in reaching my final decision. See Final Decision, page 15. Accordingly, nothing in the UGDP audit constitutes data relevant to the decision. Second, the audit did not consider the relationship between phenformin and lactic acidosis, which was the subject matter of the withdrawal proceeding. Rather, it dealt with death due to cardiovascular disease. CCD itself notes that a "most significant aspect of the audit report was that it did not directly address the validity of the study with regard to the findings concerning phenformin" (Petition at 3), and that the auditors "did not consider the study findings with regard to phenformin to be within their purview" (Petition at 4). CCD acknowledges that the only mention of phenformin in the audit conclusions concerned alleged cardiovascular mortality in one patient taking phenformin.[2] Two UGDP reported cases of phenformin induced lactic acidosis were not reviewed by the auditors. Thus, the audit considered one issue (cardiovascular mortality) and the withdrawal hearing addressed an entirely different issue (phenformin associated lactic acidosis). Therefore, the report of the auditors provides no reason to reopen the phenformin withdrawal proceeding.

CCD argues that the testimony of Bureau witnesses at the withdrawal proceeding relied upon the UGDP, and considered it to be pivotal in evaluating the safety of phenformin. CCD also notes that the Administrative Law Judge ruled that the UGDP study could serve as the basis for expert testimony even though he questioned the independent reliability of the UGDP conclusions from an evidentiary standpoint. CCD concludes that the UGDP had a pervasive influence at the hearing and affected any decision based upon the administrative record. I have already responded at length to this contention, and I disagree with it. Final Decision, Exception 3, pp, 11–15.

CCD argues that because the UGDP auditors did not review the relationship between lactic acidosis and phenformin, FDA may not apply the study for any regulatory purposes. I do not agree that FDA is required to audit every portion of the UGDP or any other study in order to use it for regulatory purposes. Any further audit or review of the UGDP findings to evaluate the data bearing on phenformin induced lactic acidosis is unlikely to alter or illuminate the

[1] The audit revealed an additional nine patients who died during the study. Thus, the original 150 audited patients became 159.

[2] With respect to this patient, the auditors agreed with CCD that the patient "probably should not have been a candidate for phenformin therapy on the basis of renal function." This conclusion is consistent with my finding that there is evidence that phenformin has been used contrary to labeled indications and that there are limitations on the ability of physicians to screen adequately for renal dysfunction. See Final Decision, Findings of Fact 22–25, pp. 52–53.

evidence in the administrative record. Whether or not fully audited, and regardless of the validity of its findings, the UGDP study was not relied on by me in withdrawing approval of the phenformin NDA's.

Finally, I note that the CCD petition for reconsideration, dated December 22, 1978, is untimely. Although the notice of availability of the final decision was published in the **Federal Register** of November 24, 1978, the decision was dated and effective on November 15, 1978. That is the "date of the decision involved" within the meaning of 21 CFR 10.33(g), which requires that a petition be filed within 30 days. Counsel for CCD was aware of the November 15 date because of their involvement in a lawsuit concerning the Secretary's imminent hazard determination on phenformin, *Forsham* v. *Califano* (D.D.C. No. 77–1478; D.C. Cir. No. 77–2072). In that suit, FDA made a specific representation to the Court that the withdrawal order would be issued on or before November 15.

I conclude that the petition for reconsideration does not merit reconsideration of my decision to withdraw the NDA's for phenformin and that the grounds presented in the petition do not meet the criteria for reconsideration set forth in the regulations, 21 CFR 10.33(d). Accordingly, the petition is denied.

Dated: February 5, 1979.

Donald Kennedy,
Commissioner of Food and Drugs.

[Docket No. 77N–0150]

[FR Doc. 79–10591 Filed 4–5–79; 8:45 am]

BILLING CODE 4110–03–M

Phenformin Hydrochloride; Withdrawal of Approval of New Drug Application; Final Decision

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs is publishing his final decision, following a formal evidentiary public hearing, findings of fact, conclusions of law, and final order on the proposal to withdraw approval of the new drug applications (NDA's 11–624 and 12–752, held by Geigy Pharmaceuticals, Division of Ciba-Geigy Corp., Ardsley, New York; NDA's 17–126 and 17–127 held by USV Laboratories, Division of USV Pharmaceutical Corp., Tuckahoe, New York) for phenformin hydrochloride under section 505(e)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e)(2). The Commissioner has determined that phenformin is not shown to be safe for use under the conditions of use on the basis of which the applications were approved. He has affirmed the Initial Decision of the Administrative Law Judge with modification and supplementation provided in his order. Introduction into interstate commerce of phenformin, except in conformity with an exemption granted pursuant to section 505(i) of the act (21 U.S.C. 355(i)), constitutes a violation of law.

EFFECTIVE DATE: November 15, 1978.

ADDRESS: The transcript of hearing, evidence submitted and all other documents cited in the decision, and the Initial Decision of the Administrative Law Judge, may be seen in the office of the Hearing Clerk (HFA–305), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Richard A. Anderson, Office of the Associate Commissioner for Health Affairs (HFY–21), Food and Drug Administration, Department of Heath, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1177.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of November 24, 1978 (43 FR 54995), the Commissioner issued a notice of availability of his final decision in this matter. Because it has been the long-standing policy of the Food and Drug Administration (FDA) to publish all notices of withdrawal of approval of NDA's, and because there has been considerable public interest in the matter, the Commissioner is now publishing the final decision in the **Federal Register.** Further, because the final decision relies very specifically on the Initial Decision of the Administrative Law Judge, the latter is also being published at this time elsewhere in this issue of the **Federal Register.** Also, a denial of petition for reconsideration is published in this issue of the **Federal Register.**

The Commissioner advises that although this document contains minor editorial changes from the final decision, such changes are made only to comply with document drafting guidelines issued by the Office of the Federal Register. There are no substantive differences between the document that follows and the official copy of the Final Decision dated November 15, 1978.

The purpose of this proceeding is to decide whether approval of the new drug applications for phenformin should be withdrawn because phenformin has not been shown to be safe for use under the conditions of use on the basis of which the applications were approved.

I. Background

Phenformin is an oral hypoglycemic drug used in the treatment of symptomatic adult-onset diabetes. Phenformin was first approved for marketing in the United States in March 1959. Soon thereafter, reports of cases of lactic acidosis associated with the use of phenformin begin to appear in the medical literature. Lactic acidosis is a condition in which abnormal amounts of lactic acid accumulate in the blood. The rate of fatalities in cases of lactic acidosis is about 50 percent. In response to these reports, warning statements and other information were added to phenformin labeling in 1964, 1970, 1974, 1976, and January 1977.

In the **Federal Register** of May 6, 1977 (42 FR 23170), the Director of the Bureau of Drugs, FDA, proposed to withdraw the approval of the new drug applications for phenformin. The proposal stated: "This action is being taken on the basis of the clear association demonstrated between the use of phenformin and the occurrence of lactic acidosis" in diabetic patients. *Id.* "Although the true frequency of the occurrence of lactic acidosis in diabetics using phenformin cannot be determined," the relative frequency among such diabetics "is considerably higher than that being reported for any other form of treatment for diabetes." 42 FR at 23172. "Because lactic acidosis is a frequently fatal complication, because no patient population exists in whom all risk factors for this complication can always be either identified or predicted, and because of the availability of effective alternative orally administered drug products and other drug and nondrug methods for diabetic therapy, the Director [of the Bureau of Drugs] concludes that the risk of phenformin therapy outweighs any possible benefits that can be derived from its use." 42 FR at 23173.

Requests for hearing, together with supportive material, were received from Ciba-Geigy and USV, the two manufacturers of phenformin. In the **Federal Register** of August 12, 1977 (42 FR 40959), FDA announced a formal evidentiary public hearing on factual issues relating to the proposed withdrawal. A prehearing conference was scheduled for August 30, 1977. The Committee for the Care of the Diabetic (CCD) appeared in opposition to the withdrawal as a non-party participant. Prior to the notice announcing the hearing, the Secretary of Health, Education, and Welfare invoked the

imminent hazard clause of section 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), to suspend immediately approval of the phenformin NDA's (Docket No. 77N–0147). Accordingly, phenformin has not been marketed under the NDA's pending completion of these proceedings on the proposed withdrawal.

At the conclusion of the prehearing conference, the Administrative Law Judge, Daniel J. Davidson, designated the following issues to be addressed at the hearing:

1. Whether, and to what extent, the use to phenformin is beneficial in the treatment of diabetic patients for whom the drug is indicated under the conditions of use prescribed, recommended, or suggested in its labeling.

2. Whether an association has been established between the use of phenformin and the occurrence of lactic acidosis, including fatalities, in patients for whom the drug is indicated under the conditions of use prescribed, recommended, or suggested in its labeling, and what is the incidence of lactic acidosis, including fatalities, in such patients, and in the diabetic population at large.

3. Whether, and to what extent, other therapeutic modalities are appropriate and effective in treating persons for whom phenformin is indicated on the basis of the conditions of use prescribed, recommended or suggested in its labeling.

4. Whether the conditions of use prescribed, recommended or suggested in the labeling for phenformin are adequate to exclude from treatment persons for whom the drug is contraindicated as a result of the presence of factors which predispose to lactic acidosis.

5. Whether, in view of all of the above, the benefits outweigh the risks associated with use of the drug, phenformin.

By Order of August 31, 1977, the Administrative Law Judge also set times for the filing of all documentary material, and he established October 5, 1977 as the date on which the hearing would commence. The hearing began as scheduled and concluded on Octobert 7, 1977.

The Administrative Law Judge issued his Initial Decision on February 6, 1978. He found that (1) phenformin has limited short-term beneficial effects in the treatment of diabetes, (2) a strong association between phenformin and lactic acidosis has been established although its rate of occurrence "is not susceptible of quantification on this record," (3) the same degree of risk associated with the use of phenformin does not exist with other forms of therapy that are effective for treating diabetes, and (4) the labeling for phenformin is inadequate to exclude from treatment those persons for hwom the drug is contraindicated as a result of factors that predispose such persons to lactic acidosis. Initial Decision at 1, 2, 46, 47, 48. Accordingly, the Administrative Law Judge concluded that "the limited benefits of phenformin are insufficient to support a finding of safety in light of the risks attending its general marketing under the approved NDA's. Approval of the NDA's for phenformin should therefore be withdrawn * * *." Initial Decision at 2, 48.

II. Exceptions

On March 8, 1978, CCD filed 18 exceptions to the Initial Decision. Neither Ciba-Geigy nor USV filed exceptions. On March 28, 1978, the Bureau of Drugs submitted its reply to CCD's exceptions. I conclude the CCD's exceptions do not justify reversal of the Initial Decision.

1. Two exceptions question the focus of the Initial Decision on whether phenformin must be withdrawn from the market. CCD argues that the Initial Decision should have considered, and, if necessary required, revision of the labeling for phenformin. CCD contends that there are specific patient populations for whom the benefit of phenformin outweighs its risks, and that those populations can be adequately identified in revised labeling. CCD characterizes the withdrawal issue as a "self-imposed" limitation, which "severely restricted[ed] the scope of the hearing" and resulted in a prejudicial restriction on the evidence presented.

The statute established the standards for approving and withdrawing a new drug application. In either case, the data on safety and effectiveness are measured by the conditions for use prescribed, recommended, or suggested in the drug's labeling. See section 505(d) of the Act. Consistent with section 505(e)(2) of the Act, the notice of opportunity for hearing defined the issue to be decided as whether phenformin is not shown to be safe for use "under the conditions of use upon the basis of which the application were approved," [1] not whether more restrictive labeling might be drated and submitted to FDA as a supplement to the NDA.

I find no merit in the CCD contention that the Administrative Law Judge identified "a number of different patient populations for which the benefits of phenformin use outweigh any risks" and that the Initial Decision was able to "specify patient populations which need phenformin." Having discussed the claim by Ciba-Geigy and USV that operators of commercial vehicles in interstate commerce would be precluded from such employment if forced to use insulin therapy rather than phenformin, the Administrative Law Judge concluded that "limiting employment possibilities cannot preclude withdrawal of approvl of phenformin." Initial Decision at 43. Thereafter, the Administrative Law Judge speculated generally that the "temporary benefits" of phenformin could be of value in a "small number" of "unusual cases" and that certain individuals were "possible candidates" if a limited distribution system for phenformin could be established; "the need may exist for a limited distribution of phenformin to special patients under specialized controlled treatment programs." Initial Decision at 44. These remarks do not constitute a "finding" that patient populations exist for whom the benefits of phenformin in general distribution pursuant to current law "outweighs the risks."

AS the Administrative Law Judge went on to point out, such a limited distribution program "cannot be authorized within the parameters of this proceeding which is charged solely with determining the propriety of the proposed withdrawal of approval of the NDA's for general marketing of phenformin." *Id.* FDA does not currently have authority to limit the distribution of drugs through specified channels, except as a consequence of a controlled clinical investigation conducted under an exemption from the new drug application requirements of section 505(i) of the Act. *American Pharmaceutical Association* v. *Weinberger*, 377 F. Supp., 824 (D. D.C. 1974), *aff'd sub nom. American Pharmaceutical Association* v. *Mathews*, 530 F.2d 1054 (D.C. Cir. 1976). The authority provided by section 505(i) cannot be used to limit distribution of a drug so long as it is approved under an NDA. Thus, the Administrative Law Judge's discussion of limited distribution referred either to a circumstance in which the NDA for phenformin had already been withdrawn or to an amendment to current law granting FDA authority to limit distribution of approved drugs. In neither case can the discussion be construed as a "finding"

[1] Since the new drug applications include their supplements, the conditions of use against which the Administrative Law Judge evaluated the safety of phenformin are those contained in the revised January 1977 labeling.

supporting continued approval under current law.

2. Two exceptions filed by CCD concern the evaluation by the Administrative Law Judge of the long-term effectiveness of phenformin. CCD argues that the qeustion of long-term effectiveness is improper because the existence of secondary failure with phenformin has been known by FDA and thus was not "new evidence" within the meaning of section 505(e)(2) of the Act, and because many drugs presently permitted to be marketed exhibit similar decreasing effectiveness over time. CCD's position is that a loss of effectiveness over time does not render a drug either legally or medically ineffective.

I find that the extent of effectiveness over time is a valid consideration. Adult onset diabetes is a chronic conditions with severe complications. Since the disease requires long-term rather than intermittent management, it is relevant to inquire into the duration of the treatment. The management of a disease may involve a variety of treatments, some of which are more useful during a particular stage. A drug is not unsafe or ineffective simply because it constitutes only a portion of the treatment regimen either in terms of concomitant therapy or time. Nevertheless, a risk to benefit evaluation of any treatment must include an evaluation of the extent of the benefit.

CCD's assertion that FDA knew of secondary failure with phenformin before approval of the NDA's is incorrect. In fact, significant evidence on the question of secondary failure associated with phenformin was developed only in the context and for the purposes of the evidentiary hearing. See CG–61, and Bureau of Drugs Brief, 59–70. In addition, "new evidence" includes a reevaluation of any evidence previously submitted. *Bell* v. *Goddard*, 366 F. 2d 177 (7th Cir. 1966).

3. Three of the CCD exceptions deal with the University Group Diabetes Project Study (UGDP), a long-term prospective clinical trial carried out in the 1960's. The CCD criticized the Administrative Law Judge's admission of the UGDP study results (B–395, B–396) into evidence without requiring disclosure of the raw data (individual reports on all of the individuals who participated in the study). See Order of November 11, 1977, denying CCD's Motion to Strike Or, In The Alternative, To Produce Evidence. CCD argues that the failure of the Administrative Law Judge to require that raw data be filed by the Bureau of Drugs pursuant to 21 CFR 12.85 invalidates the hearing procedure and its results. CCD also takes exception to the UGDP study because it believes the study "has been thoroughly impeached" from an evidentiary, scientific and medical veiwpoint. CCD objects to the decision of the Administrative Law Judge to permit expert opinion testimony concerning the safety and effectiveness of phenformin based upon the UGDP study. Initial Decision at 7. CCD argues that reliance upon the UGDP by Bureau of Drugs witnesses was substantial and that those experts were biased because they had been associated with the study. CCD also alleges that retrospective studies admitted into evidence and relied upon by the Administrative Law Judge followed upon and were influenced by the results of the UGDP study. CCD concludes that by failing to strike the UGDP study or to consider its impact or other evidence, the Administrative Law Judge's Initial Decision is "flawed and not based on substantial and reliable evidence" and that his ruling "invalidates the hearing process."

I affirm the Administrative Law Judge's ruling on the motion to strike the UGDP data. The Administrative Law Judge held that the "lack of availability of underlying data casts considerable doubt on the reliability of the UGDP conclusions from an evidentiary standpoint. To the extent such data was not made available, the UGDP conclusions cannot be considered as substantiated on the record." *Id.* Accordingly, in reviewing the Bureau's evidence on the question of safety, the Administrative Law Judge referenced the UGDP study in only one paragraph of his 8-page summary. Initial Decision, at 20.

The Administrative Law Judge concluded that the UGDP study could be used for two purposes: to raise questions about the safety of phenformin and as the basis for expert opinion. The FDA has long taken the position that evidence suggestive of a lack of safety may be considered in evaluating whether a drug has been shown to be safe even though the evidence does not meet the standards required to establish the safety of the drug. The Administrative Law Judge's ruling that the UGDP study might serve as the basis for expert testimony is supported by Rule 703 of the Federal Rules of Evidence, which provides that even if data are not admissible into evidence they may nevertheless form the basis of opinions by experts if they are the type of data reasonably relied upon by experts in that particular field. See *Nanda* v. *Ford Motor Co.*, 509 F. 2d 213 (7th Cir. 1974); *Jenkins* v. *United States*, 307 F. 2d 637 (D.C. Cir. 1962). Experts routinely keep abreast of the literature and base their opinions, in part, on published reports of drug studies. They rarely see or review the "raw data." Nor are they required to base their expert opinions on raw data; any such conditions would require expert witnesses to disregard the vast bulk of their expert knowledge.

The record in this proceeding includes nearly 400 articles published in the medical literature. Many of them report studies on phenformin. None of those articles is accompanied by the "raw data" upon which it is based. The Bureau has relied solely on the published report of the UGDP study in the same way that is has relied upon the other published articles that were admitted into evidence. 21 CFR 12.85 requires only that the Bureau provide data upon which it relies; it does not require the Bureau to submit related data on which it does not rely.

Because of CCD's emphasis on the unavailability of the raw data underlying the UGDP study, I have reviewed the testimony of the Bureau of Drugs' expert witnesses and find that their reliance upon the UGDP study was not substantial and cannot reasonably be characterized as pivotal to the opinions expressed by those witnesses.

I reject the suggestion by CCD that the witnesses who testified for the Bureau of Drugs consisted primarily of those persons whose professional reputations would be tarnished if the UGDP study were ever established to have been faulty. The CCD exception provides no specific basis upon which to question the professional integrity of the Bureau's witnesses. Their curricula vitae strongly support the Bureau's reliance on their professional opinions. See B–464, B–466, B–468, B–470, B–472, B–474, B–476, B–478, B–480, B–482, B–484, B–486, B–488, B–492, B–494, B–496, B–498, B–500. Challenges to scientific integrity of the sort made by CCD in this case, certainly cannot be accepted without any support in the record.

I am aware of the controversy over the UGDP study. *Bradley* v. *Weinberger*, 483 F. 2d 410 (1st Cir. 1973). Indeed, during the course of this proceeding, FDA participated in an audit of the UGDP data. Because the audit coincides with this withdrawal proceeding, and is not part of this record, I have not considered the UGDP study in reaching my final decision. References to the UGDP study in the substantive portion of the Initial Decision are not adopted.

4. CCD takes exception to the ruling of the Administrative Law Judge admitting

into evidence foreign clinical data submitted by the Bureau of Drugs. CCD contends that the data do not satisfy the requirements of 21 CFR 312.20, and concludes that the Administrative Law Judge applied a double standard for the admission of evidence, whereby controlled clinical studies are required to support an NDA while technically incomplete studies, which would not support a showing of safety or effectiveness, were considered as part of the "overall body of available safety data."

I affirm the decision of the Administrative Law Judge that data that do not meet the requirements of 21 CFR 312.20 nevertheless may be considered in evaluating drug safety. See **Federal Register** of November 19, 1976 (41 FR 51215). The "double standard" complained of by CCD is the standard contemplated by the statute.

I believe, however, that the statement of the Administrative Law Judge that foreign clinical data do not qualify as prima facie evidence of a lack of safety (Initial Decision at 8) should be modified. Although failure of foreign clinical data to meet the requirements of 21 CFR 312.20 may affect their weight in evaluating a drug's safety, this does not mean that they cannot be the basis for a prima facie case that a drug is not safe. I find that a prima facie case for withdrawal or non-approval under section 505 of the Act can be made on the basis of medical facts reported in foreign literature, such as the reports of birth defects resulting from use of thalidomide in Europe. See S. Rept. No. 1744, 87th Cong., 2d Sess., 40 (1962).

5. CCD takes exception to the weight given by the Administrative Law Judge to the testimony of certain diabetologists appearing on behalf of Ciba-Geigy and USV on the question of the safety of phenformin. CCD claims that the Administrative Law Judge disregarded the testimony of these experts because it conflicted with evidence, primarily retrospective studies on cases of lactic acidosis, that CCD believes is not of comparable value. According to CCD, the Administrative Law Judge's evaluation of the testimony of the manufacturers' experts reveals that he had prejudged the case. CCD also takes exception to the Administrative Law Judge's failure to give substantial weight to Ciba-Geigy's nationwide survey of reports of lactic acidosis among patients treated with phenformin.

The Administrative Law Judge found that the Ciba-Geigy data on the rate of incidence of lactic acidosis (CG–26) are deficient due to (1) the recognized phenomenon of under reporting of adverse effects to drug companies, (2) the tendency of reports in the medical literature to decline once a discovery has been published repeatedly, (3) deficiencies in the criteria used by Ciba-Geigy to screen the data, (4) the inadequacy of the qualifications of the Ciba-Geigy employee who prepared the data, and (5) the absence of a showing by Ciba-Geigy that an effort was made to supplement information that was inadequate and resulted in exclusion form the study of certain reports of lactice acidosis. Initial Decison at 22–26. The Administrative Law Judge "disregarded" the data in that he concluded that they were flawed to such an extent as to preclude their being afforded "any significant evidentiary weight." *Id.* at 26. On the basis of my independent consideration of the record, I affirm the findings of the Administrative Law Judge with respect to the Ciba-Geigy study.

The Administrative Law Judge did not disregard the testimony of the Ciba-Geigy expert diabetologists. Rather, he concluded that their testimony that they had not seen lactic acidosis in their patients was not determinative of the safety of phenformin under general maketing conditions. Several of these experts testified about their knowledge of lactic acidosis in patients other than those under their private care. The majority of diabetics in this country are not treated by expert diabetologists. Initial Decision at 26–28. The Administrative Law Judge concluded, in light of the overall evidence of lactic acidosis associated with phenformin, that the very testimony that phenformin is safe when prescribed by "the most eminent" diabetoligists in the United States suggests that patients for whom phenformin is prescribed by general practitioners run "a considerable risk of phenformin-associated lactic acidosis." *Id.* at 28.

6. In a related exception, CCD objects to the Administrative Law Judge's conclusion that proof of the safety of phenformin when administered by specialists is insufficient to justify its continued general marketing. CCD argues that this standard is not sanctioned by law and that the evidence does not support a finding that some physicians with certain training can administer phenformin while others cannot. CCD urges that the Administrative Law Judge cannot base a decision upon factors beyond the scope of FDA's authority.

CCD has misconstrued the statutory requirement of safety and the Admininstrative Law Judge's reasoning. Section 505(d)(1) requires that a new drug be "safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof." The statute thus requires general safety for use—that is, safety for use by the general practitioners who do or will use the drug. The Administrative Law Judge found that on the record before him phenformin was not shown to be safe as required by section 505(d)(1). He also noted evidence tending to show that phenformin is safe when prescribed by expert diabetologists. He correctly interpreted section 505(d)(1), however, as requiring a broader showing of safety. In light of the entire record concerning the actual use of phenformin, the evidence tending to show that phenformin may be prescribed safely by expert diabetologists does not establish the general safety require by section 505(d)(1).

CCD's argument would have merit if FDA had authority to leave phenformin on the market by restrict its distribution to the prescription of expert diabetologists or to the prescription of physicians with patients for whom phenformin is appropriate. As Ciba-Geigy and USV recognize, however, FDA does not have such authority. Initial Decision at 28; Ciba-Geigy/USV Brief at 18. Having found that phenformin was not shown to be safe for use by those persons who, pursuant to state law, are licensed to prescribe it and treat diabetic patients, the Administrative Law Judge was required to recommend withdrawal of the NDA's for the general marketing of phenformin.

7. CCD takes exception to the text of a draft **Federal Register** notice of the availability of phenformin pursuant to an investigational new drug exemption (IND). CG–81. (This draft was not admitted into evidence. Initial Decision at 44, n. 5.) CCD alleges that the draft is inconsistent with the position taken by the Bureau of Drugs because the Bureau's notice of opportunity for hearing and its position in this proceeding support the complete withdrawal of phenformin, while the existence of the Bureau-approved IND demonstrated the phenformin can be marketed and distributed under certain controls. CCD concludes that the Bureau'a separtate actions are conflicting and that the supposed inconsistency "invalidates any results of the administrative proceeding."

This exception is without merit. First, no notice based upon the draft IND document has ever been published in the **Federal Register**. Second, it is not inconsistent for the Bureau to support

the withdrawal of approval of phenformin for general marketing while recognizing that an investigational new drug exemption may impose controls that render the use of the drug acceptable and may yield safety data that do not now exist. The Bureau routinely approves IND's for drugs that are not subject to approved NDA's. Thousands of drugs have been so regulated. Indeed, the very purpose of an IND is to authorize a limited investigation of an as yet unapproved use of a drug. There is no legal difference between and IND for a drug that has never been the subject of an approved NDA and an IND for a drug that has.

8. Noting that the Administrative Law Judge held that the rate of occurrence of phenformin-associated lactic acidosis is "not susceptible of quantification on this record," the CCD argues that the Bureau of Drugs has not sustained its burden.

There is an important distinction between a requirement of mathematical quantification of a rate of occurrence of lactic acidosis and the burden to adduce new evidence which, when evaluated together with other data, raises "significant doubts as to the appropriateness of the finding of a prior showing of safety in light of the new evidence." Initial Decision at 5. Although unable to quantify the rate of occurrence of lactic acidosis, the Administrative Law Judge found that lactic acidosis "occurs virtually exclusively among phenformin users," and that the absence of a base rate of lactic acidosis in the diabetic population generally, which is needed to calculate the rate of lactic acidosis among phenformin users, "is typical of many diseases and does not detract from the demonstration of a strong association between phenformin and lactic acidosis." See Initial Decision at 46. On the basis of my independent evaluation of the record, I find that the association between the use of phenformin and the occurrence of lactic acidosis is real and has been substantiated in this proceeding.

9. CCD objects to the ultimate finding of the Administrative Law Judge that other treatment are just as effective as phenformin but do not present the same degree of risk. CCD's objection is on the ground that the testimony of significant side effects associated with the use of insulin was disregarded.

I reject CCD's characterization of the record. The phenformin labeling, B–506(n), states that diet and insulin are the therapies of choice in the control of diabetes. Although there are side effects from treatment with insulin, its overall effectiveness in treating the chronic complications of diabetes was found to be substantial. Initial Decision at 41. The references in the record to the existence of side effects of insulin therapy were not disregarded by the Administrative Law Judge; on balance, they simply did not outweigh the evidence of its efficacy, or require a conclusion that insulin is less safe than phenformin.

10. CCD alleges that the Administrative Law Judge "has not properly taken into account the compliance problems inherent in both diet and insulin therapy." CCD claims that these considerations were "frequently stressed in the testimony of CCD and Ciba-Geigy witnesses" and were not given due weight by the Administrative Law Judge.

This assertion is not supported by the record. The Administrative Law Judge found that the "major difficulty encountered in this mode of therapy [diet] has been in effecting compliance with the diet regimen." Initial Decision at 40. Likewise, he recognized the problems with self-administration of insulin. See Initial Decision at 43, 44. The Administrative Law Judge was apparently impressed, however, with the testimony of one witness that "* * * when the advantages of insulin therapy were thoroughly explained to patients for whom diet proved unsuccessful, there was not a single refusal of insulin therapy (Tr. 8)." Initial Decision at 41.

This exception is also rejected because it fails to cite the specific portions of the record on which it relies. Unlike the CCD exception, the Administrative Law Judge cited specific portions of the record in discussing both the problems and successes with diet and insulin regimens. Initial Decision at 40–44. See 21 CFR 12.125(b), which provides that exceptions to the initial decision shall contain "specific reference to those parts of the record upon which the exceptions are based."

11. One CCD exception is based on CCD's view that the Administrative Law Judge "simply restated the contents of these studies [Submitted by the Bureau of Drugs] without critical comment * * * without differentiating what is important and reliable from that which is of minimal reliability." According to CCD, this causes the decision to be arbitrary and capricious and not supported by substantial evidence.

The objection is without merit. In his introductory remarks in that portion of the Initial Decision entitled "Bureau's [safety] Evidence," the Administrative Law Judge reviewed the criteria suggested by Ciba-Geigy for eliminating bias from study reports, and found that "the [Bureau] studies of Dr. Tranguada, Dr. Fullop and Dr. Brach, et al., do meet this Ciba-Geigy criteria." Initial Decision at 14. The Administrative Law Judge placed primary reliance upon these studies, which he found to be "the best available in the record." Initial Decision at 22.[2]

12. CCD alleges that the Secretary's Suspension Order and the Administrative Law Judge's Initial Decision are based on entirely different data and that the data relied upon by the Secretary were not given great weight by the Administrative Law Judge. CCD concludes that the differences establish that the data relied upon by the Secretary in the suspension decision are unreliable.

The Secretary's Suspension Order and the Administrative Law Judge's Initial Decision are not based upon "entirely different data." The four specific items referenced in the CCD exception—the UGDP study, the foreign clinical data, the manufacturer's data, and data supplied by Dr. Davidoff—are common to both proceedings. The FDA submissions to the Secretary in the suspension proceeding, however, were stricken from the record in this proceeding. Because the Suspension Order is a separate proceeding, and because of the pending litigation involving the propriety of the Secretary's invocation of the imminent hazard provisions of the Act, *Forsham* v. *Califano*, 442 F. Supp. 203 (d. D.C. 1977), appeal pending (D.C. Cir.) (No. 77–2072), it would be inappropriate for me to make a detailed comparative analysis of the data presented in these independent proceedings.

I note, however, that the criteria for invoking the imminent hazard provision and those for withdrawing a new drug application are different. Accordingly, it is to be expected that the records of the two proceedings would contain different data.

13. CCD takes exception to the order of the Administrative Law Judge that denied, without prejudice, a motion of CCD pursuant to 21 CFR 12. 89(d) to obtain rights additional to those prescribed for non-party participants. See Order of September 26, 1977; see also Initial Decision at 8–9. CCD argues that it represents interests different from

[2] Although compliance with these criteria could not be determined for other studies, the Administrative Law Judge held that "this does not mean that such studies may not be considered for purposes of raising questions as to the safety of phenformin and as corroboration for similar conclusions reached in the other studies." Initial Decision at 14. The fact that he did not find it necessary to evaluate these other studies critically does not render his decision arbitrary.

those of the Bureau of Drugs and the manufacturers. CCD concludes that the Administrative Law Judge's decision to deny additional rights of participation rests upon "the underlying faulty assumption that basic due process rights may be denied CCD in the discretion of the hearing officer."

Requests for hearing in response to the May 6, 1977 notice were filed by Ciba-Geigy and USV. Accordingly, the NDA holders, together with the Bureau of Drugs, were designated as the parties to the hearing. The CCD did not announce its desire to participate until three days after the expiration of the period for filing notices of non-party participation. Transcript of August 30, 1977 Prehearing Conference at 4, 35–37. CCD was not entitled to greater procedural rights than those accorded it in the proceeding.

Participant rights in formal evidentiary hearings are established by regulation, 21 CFR 12.89(b), and include the right to submit written testimony and documentary evidence, to file briefs, written objections, and other pleadings; and to present oral argument. CCD requested an opportunity to submit written interrogatories and to conduct crossexamination. Due to the expedition with which the hearing was held, in light of the Secretary's suspension order, the use of written interrogatories was not sanctioned for any participant, including the parties. With respect to the request to conduct cross-examination, the Administrative Law Judge's ruling permitted CCD to renew its request on a witness-by-witness basis. See Order of September 26, 1977. Thus, CCD was not prejudiced by its status as a non-party participant.

CCD's allegation that its interest and those of physicians and patients using phenformin were not adequately represented by the manufacturers is not supported by the record. CCD documentary evidence consisted of the affidavits of seven expert witnesses, five of whom also submitted testimony on behalf of Ciba-Geigy. Compare CCD exhibits 1, 3, 4, 5, and 7 with Ciba-Geigy exhibits 2, 3, 5, 9, 14, 16, 17, 42, 61, and 66. In addition, the manufacturer parties vigorously contended that a patient population exists justifying the continued marketing of phenformin under the restrictive January 1977 labeling. This contention appears to be the heart of the CCD position. The argument that CCD has no investment in the existing labeling and "therefore can present a position without a predetermined bias" is not compelling since labeling other than that approved in the new drug applications and their supplements is not at issue in this withdrawal proceeding.

The granting of additional rights of participation rests within the sound discretion of the Administrative Law Judge and is based upon an evaluation of whether a participant's interest will not be adequately protected otherwise or whether broader participation is required for a full and true disclosure of relevant evidentiary facts. 21 CFR 12.89(d). In view of the breadth of the presentation by Ciba-Geigy and USV, the substantial overlap of their witnesses with those of CCD, the inapplicability of the question of substitute labeling, together with the provision of the Administrative Law Judge's order for request to cross examine specific witnesses, I cannot conclude that the Administrative Law Judge abused his discretion in denying CCD's request. I also note that there is no "right" granted by the statute to a person who is not the holder of an NDA to participate in a withdrawal proceeding in any capacity. Participation status is granted by FDA in the exercise of its descretion any may, therefore, be limited as the agency believes appropriate. The exception is rejected.

III. Review of the Initial Decision

A. Burden of Proof

I adopt the holding of the Administrative Law Judge, Initial Decision at 4–7, that section 505(e)(2) requires the Bureau of Drugs to bear the initial burdern of adducing new information that, when evaluated together with the information available when the new drug applications for phenformin were approved, shows that phenformin is not shown to be safe for use under the conditions of use upon the basis of which the applications were approved. To meet that burden, the Bureau "need only raise significant doubts" as to the prior showing of safety. Once this threshold burden is met, the manufacturers are required to prove the safety of phenformin.

I agree with the Administrative Law Judge that the statutory reference to new information "cannot reasonably be construed as only that evidence that came to light subsequent to the date of the approval of the most recent supplemental NDA," so as to preclude the reevaluation of the evidence previously available. In addition to the reasons set forth in the Initial Decision, I find that the application of *Hess & Clark* v. *FDA*, 495 F.2d 975 (D.C. Cir. 1974), to a withdrawal under the new drug provisions is supported by the legislative history of the new animal drug provisions of the Act, S. Rep. No. 1308, 90th Cong., 2d Sess., 5 (1968)[3] and that the Administrative Law Judge's definition of the Bureau's burden is supported by the legislative history of the 1962 amendments to section 505(e). See Cong. Rec. 10105–10108 (June 11, 1962); S. Rep. No. 1744, 87th Cong., 2d Sess, 25–26 (1962); Committee on the Judiciary, 87th Cong., 2d Sess., 13, 37 (Committee Print 1962), Cong. Rec. 16302–16304 (Aug. 23, 1962); Section 102(d) of House Bill 11581; H.R. Rep. No. 2464, 87th Cong., 2d Sess. 1–8, 16 (1962), Cong. Rec. 19890–19895 (Sept. 27, 1962), H.R. Report No. 2526, 87th Cong., 2d Sess., 19 (1962). See also *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973), *North American Pharmacal, Inc.* v. *Department of Health, Education, and Welfare*, 491 F.2d 546, 551, (8th Cir., 1973), and *Ubiotica Corp.* v. *FDA*, 427 F.2d 376, 378 (6th Cir., 1970).

The Administrative Law Judge measured the cut-off period for new evidence by the January 1977 labeling. See Initial Decision at 4, 5. However, Ciba-Geigy and USV state that the last approval of a supplement to the new drug applications was granted in June 1976, in conjunction with the June 1976 labeling. Ciba-Geigy/USV Brief at 63–66. If one takes the manufacturers' date, it becomes even clearer that there is new evidence, not previously available, upon which it can be found that phenformin is no longer shown to be safe. For example, due to a time lag in reporting, some of the reports of lactic acidosis in 1975 and 1976 (CG–26) were unavailable in June 1976 but were available by January 1977.

B. Position of Participants

The Administrative Law Judge's preliminary summary of the position of the parties accurately reflects the evidence and arguments presented by them at the proceeding.

With respect to the position of CCD, I adopt the summary in the Initial Decision at 8–9, as modified by my response to the CCD exception, para. 13, at 26–29, *supra*.

C. Basic Mechanisms of Phenformin Activity

In response to the position taken by Ciba-Geigy and USV, the Administrative Law Judge found that section 505(e)(2) does not require that the Bureau establish "a plausible biomedical

[3] The withdrawal provision for new animal drugs was derived from and is nearly identical to the correspohding provision for new drugs. See *Agri-Tech, Inc.* v. *Richardson*, 462 F.2d 1148, 1150 (8th Cir. 1973).

explanation as to why such elevations [of blood lactate levels] occur" before phenformin may be shown not to be safe. Initial Decision at 9. The Administrative Law Judge reasoned that since establishment of clearly defined mechanisms of action is not required to prove the effectiveness of a drug, its absence does not preclude consideration of a lack of safety. Mechanisms of action have not been identified for certain drugs marketed subject to approved new drug applications. This, of course, is not a desirable situation but reflects certain limits, both technical and ethical, on the extent to which biomedical research may establish pharmacological modes of activity in human subjects. As a result of these constraints, there are many drugs where the precise mechanism of action is unknown.

I affirm the Administrative Law Judge's statement of the law.

I affirm with the Administrative Law Judge's finding that "there is substantial evidence relating to mechanisms of action of phenformin" and that although scientific research "is not totally definitive, it does provide a probable explanation for the occurrence of lactic acidosis" associated with phenformin. Initial Decision at 9, 12.

D. Safety Evidence

The Administrative Law Judge summarized the manufacturers' position as follows:

> Ciba-Geigy claims that no scientifically valid conclusions concerning an association between phenformin and lactic acidosis can be drawn by simply aggregating cases of lactic acidosis during phenformin therapy, without reference to (a) existing label restrictions, (b) the background occurrence of lactic acidosis in the patient population in question, or (c) the various bias factors typically accompanying retrospective (or even prospective) searches for an adverse reaction. Initial Decision at 13.

The Administrative Law Judge gave careful consideration to the factors identified by Ciba-Geigy, although he disagreed with the company's proposed conclusion that the Bureau's evidence does not establish an association between phenformin and lactic acidosis. He found however, that the rate of occurrence of lactic acidosis associated with the use of phenformin "is not susceptible of quantification on this record." Initial Decision at 1, 47. The Administrative Law Judge recognized the shortcomings in gathering adverse reaction reports, and he gave greater weight to those reports that met the guidelines suggested by Ciba-Geigy. See Initial Decision at 14, 22–25.

The approval or withdrawal of a new drug application is made with reference to the conditions of use prescribed, recommended or suggested in the drug's labeling. However, section 505(e)(2) specifically provides that the evidence of a lack of safety must be "evaluated together with the evidence available * * * when the application was approved." Thus, experience with a drug prior to its current labeling is relevant to a withdrawal proceeding under this section of the Act. One of the issues established for resolution in this proceeding was:

> (4) Whether the conditions of use prescribed, recommended, or suggested in the labeling of phenformin are adequate to exclude from treatment persons for whom the drug is contraindicated as a result of the presence of factors which predispose to lactic acidosis.

The Administrative Law Judge found that the January 1977 labeling, particularly the contraindications designed to prevent the use of phenformin by diabetics with conditions that predispose them to develop lactic acidosis, was inadequate because a reasonable expectation does not exist that the labeling could and would be followed. The Administrative Law Judge also found that lactic acidosis occurred even among those patients taking phenformin at the daily dose established in the January 1977 labeling and for whom predisposing or contraindicated conditions do not exist.

Upon review of the entire administrative record, I find that the Bureau met its burden of establishing that phenformin is no longer shown to be safe. Initial Decision at 15–22. I agree with the Administrative Law Judge that "there can be no doubt an association exists between phenformin and lactic acidosis" (Initial Decision at 22) and that the association exists even in cases of compliance with the January 1977 labeling (Initial Decision at 18, 22, 32–33).

The Ciba-Geigy data offered to establish the safety of phenformin consisted primarily of a review of cases of lactic acidosis associated with phenformin reported in the United States literature or directly reported to the manufacturer and the testimony of expert diabetologists "which shows that within the group of patients under their care, there is virtually no incidence of lactic acidosis associated with phenformin therapy." See Initial Decision at 22–29. See also CG–1–22, CG–26, CG–51, B–59.

The Ciba-Geigy study of adverse reactions (CG–26) was found by the Administrative Law Judge to "suffer from several defects." For this reason, he concluded that the study "cannot qualify as a reasonable determination of the total number of phenformin-associated lactic acidosis cases occurring in the United States. A fair view of this study demonstrates it to be flawed to such an extent as to preclude its being afforded any significant evidentiary weight * * *." Initial Decision at 26. For the reasons stated by the Administrative Law Judge, as supplemented by my Findings of Fact, para. 27, I agree with this conclusion.

Ciba-Geigy submitted into evidence the testimony of diabetologists who have had "extraordinary success" (*id.*) in administering phenformin without observing lactic acidosis. These witnesses have "never seen a case of phenformin-associated lactic acidosis in patients under their care." The Administrative Law Judge found that "considering the large number of patients treated by these diabetologists without any incidence of lactic acidosis, the rate of occurrence in this population is extremely small." *Id.* However, the Administrative Law Judge concluded (Initial Decision at 29):

> Nevertheless, proof of the safety of phenformin when administered by specialists is insufficient to justify continued approval of phenformin because the majority of diabetics are treated by their primary physicians rather than specialists (Tr. 116–117). If phenformin is to enjoy continued marketing, it will be available to all physicians without regard to their expertise or experience. If doctors are unable to prescribe phenformin without endangering the lives of their patients, the low risk of danger of this drug when in the hands of an expert does not *a priori* justify its continued marketing. The FDA is, as stated by Ciba-Geigy and USV, powerless to limit approval of a drug only to administration by specialists. Therefore, if phenformin is unsafe when administered by generalists because its risk to the American public at large is greater than its benefit, its approval must be withdrawn.

The expert testimony submitted by Ciba-Geigy does not establish the safety of phenformin for general continued marketing under an NDA. See my response to CCD exceptions, paras. 5 and 6 at 16–20, *supra*. I adopt the Administrative Law Judge's finding as supplemented by my Findings of Fact, para. 30.

E. Detection of Predisposing Factors/ Inability to Comply With Label Requirements

In considering the adequacy of the phenformin labeling, the Administrative Law Judge summarized the contention of the manufacturers and then stated his view of the proper test of compliance:

Ciba-Geigy and USV suggest that the adverse effects of phenformin therapy occur only when patients have some deficiency which predisposes them to lactic acidosis. They view these adverse effects as avoidable by testing the patient for these factors prior to administration of the drug (Ciba-Geigy-USV Brief at 55). To substantiate this argument, it must be shown that the preexisting condition would have been diagnosed at the time the drug was prescribed using methods that are likely to be part of the usual practice of medical community. Furthermore, it must be shown that any development of these predisposing factors after treatment would be identified and would result in the withdrawal of the medication before the onset of lactic acidosis. Initial Decision at 29.

I adopt this statement of the test of compliance with phenformin labeling.

The Administrative Law Judge noted that there are differences of opinion among experts as to the methods adequate for identifying those persons who are predisposed to develop lactic acidosis and who, therefore, are contraindicated for its use under the January 1977 labeling. However, he found the evidence adduced by the Bureau of Drugs to be more persuasive. With respect to screening for impaired renal function, the Administrative Law Judge concluded that "compliance with the label requirements at the primary physician level or with the consistency in the practice of specialists is unlikely to prevent the occurrence of lactic acidosis." Initial Decision at 31. With respect to liver disease, another contraindication for phenformin therapy, he found that "time and cost considerations cause primary physicians to do a less than thorough workup for liver disease prior to prescribing phenformin * * *. Therefore, severe but chronic liver damage is likely to remain undetected." *Id.* I also find, on the basis of the record developed in this proceeding, that screening practices routinely performed on diabetic patients will not assure detection of patients for whom phenformin is contraindicated. See Initial Decision at 29–32.

The manufacturers asserted that phenformin's effects should be considered only with regard to those patients meeting the present label requirements. While acknowledging that section 505(e) measures safety in terms of conditions of use prescribed in a drug's labeling, not under actual conditions of use, the Administrative Law Judge also found substantial evidence of noncompliance with prior labeling restrictions. He reasoned:

> The principal difficulty is that the general practitioners who care for the majority of adult-onset diabetics would be unable in their normal practice to discover the existence of all predisposing factors of lactic acidosis and would therefore be unable to comply with the conditions of use prescribed, recommended, or suggested in the [current] labeling.
>
> * * * * *
>
> * * * Available tests are generally unable to rule out renal and hepatic insufficiency.* * *
>
> * * * * *
>
> * * * [The phenformin labeling cannot] reasonably be expected to result in the desired limitation of the population to which it will be administered.
>
> * * * * *
>
> Although the prescription of a drug outside of its package recommendation would not, *per se*, be considered as prima facie evidence as to its lack of safety for the purpose of withdrawal of approval of an NDA, the widespread use of a drug contrary to the label requirements should not be ignored. This is particularly true when the prescription practices outside of label requirements are widespread, predictable and substantiated by epidemiological trends in evidence.
>
> * * * * *
>
> * * * The majority of lactic acidosis cases associated with phenformin therapy reported to Ciba-Geigy were eliminated from consideration in the Ciba-Geigy study on the basis that the administration of the drug was not within the confines of the label requirements. It therefore appears that there are many cases of the American medical community not complying with the label requirements when prescribing phenformin. Initial Decision, 34–37.

The question of physician compliance with labeling restrictions has been of great concern to FDA and the entire medical community. See Initial Decision at 36–37. Additional doubts arise when labeling is new, prescribing patterns under it are not known, and previous label restrictions have not enjoyed a uniformly high degree of compliance. The manufacturers, however, bear the ultimate burden of proving safety under current labeling. The Administrative Law Judge found that the conditions of use prescribed in January 1977 labeling are "inadequate to preclude from treatment [with phenformin] those persons for whom the drug is contraindicated." Initial Decision at 1, 47.

There have been numerous changes in phenformin labeling in recent years. See B–506 and CG–25. The 1970 labeling contained a lactic acidosis warning and reference to related contraindications, including the major predisposing factors listed in the current labeling. Ex. E to CG–25. The 1974 and 1976 modifications were even more severe in warning of lactic acidosis and designating conditions predisposing to lactic acidosis. See Exs. P and N to CG–25. The 1970–1976 labeling has been inadequate to prevent misprescribing as demonstrated by evidence of the use of phenformin in contraindicated persons. Much of the evidence of this contraindicated use comes from Ciba-Geigy's own data (CG–26). Due to the time lag in reporting known cases of lactic acidosis and underreporting generally, this evidence applies primarily to practices under pre-January 1977 labeling.

However, the Administrative Law Judge concluded that the January 1977 labeling is, as a practical matter, "not susceptible to a high degree of compliance and cannot reasonably be expected to be closely followed by physicians" (Initial Decision at 37), even though experience with the new labeling has not been extensive. For physicians to be able to follow the January 1977 labeling, they would have to be able to identify those patients for whom phenformin is contraindicated. Most physicians who prescribe phenformin cannot do that. Due to inadequate screening, those persons most at risk cannot be identified. Due to the appearance of lactic acidosis among patients with no predisposing conditions, even properly screened patients are at risk. Consequently, the current labeling has not been proven to be adequate. Therefore, I adopt the Administrative Law Judge's discussion (Initial Decision at 34–37).[4]

F. Risk/Benefit.

I adopt the Initial Decision (37–42). I find also that the evidence of the effectiveness of phenformin must be considered together with the inability of physicians to routinely demonstrate which portion of concomitant therapy is responsible for a perceived beneficial effect, and the infrequency of periodic testing to determine whether the effect is sustained for as long as it appears to be.

The benefit/risk assessment should include a ruling on the assertion by Ciba-Geigy and USV that phenformin is particularly useful for those diabetics with an excess of insulin and for whom additional insulin is therefore not a appropriate treatment. I find this claim to be unsupported on the record in this proceeding. See Findings of Fact, para. 32.

---

[4] The Administrative Law Judge suggests that the phenformin labeling is so "vague" (Initial Decision at 35) as to preclude a reasonable expectation of compliance. If he was taking exception to the phraseology used to describe the contraindications, I disagree, and do not adopt this particular finding. The Administrative Law Judge also suggested that prescription practices outside of phenformin labeling have been "predictable." (*Id.*) I agree to the extent that persons predisposed to lactic acidosis cannot be predicted under the current labeling.

G. Patients for Whom Benefit of Phenformin Therapy May Outweigh Risks.

The purpose of this proceeding is to determine whether phenformin is shown to be safe for general marketing under the conditions prescribed, recommended, or suggested in its labeling. See my response to CCD exception, para. 1 at 7–10, *supra*. The existence of a more limited patient population for whom the benefits of phenformin therapy may outweigh the risks is not at issue. *Id.* The question of a voluntary, limited distribution program raised in the Secretary's suspension order is also not part of this proceeding.

For these reasons and in view of pending litigation concerning the propriety of the Secretary's invocation of the imminent hazard provisions, I do not adopt this section of the Initial Decision (at 42–44) but rather find as follows: The effect of withdrawal of phenformin on certain employment opportunities of diabetics does not preclude a decision that phenformin has no longer been shown to be safe. Limitations on occupational options because of health problems are not unique. Because phenformin is not currently labeled for use in only those patients who are allergic to insulin or unresponsive to desensitization, such use for that population is not an issue in this proceeding; and even a finding of safety for such use would not constitute a finding of general safety for use under phenformin's labeling and would not be sufficient to avoid withdrawal.

H. CCD Witnesses.

I adopt the Administrative Law Judge's summary of the CCD data submitted in this proceeding. See my response to CCD exception, para. 13 at 26–29, *supra*.

I. Discussion and Conclusions/Ultimate Findings and Order.

Having made reference to the administrative record throughout his opinion, the Administrative Law Judge summarized the evidence, without citation, and stated his conclusions and findings with respect to the issues designated at the August 30 prehearing conference. See Initial Decision at 45–48. I am issuing Findings of Fact, Conclusions of Law, and a Final Order. In most instances, these will supplement the discussion, conclusions, and findings of the Initial Decision. However, to the extent that my findings are inconsistent with those of the Administrative Law Judge, the Initial Decision is superseded. As modified by my Findings of Fact, responses to CCD exceptions and comments on the Initial Decision, contained in this order, the Initial Decision is adopted and made a part of the final order.

IV. Findings of Fact and Conclusions of Law.

A. Findings of Fact.

1. Phenformin hydrochloride (phenformin) is a new drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p), which has been shipped in interstate commerce pursuant to new drug applications filed by Geigy Pharmaceuticals, Division of Ciba-Geigy Corporation (NDA's 11–624 and 12–752), and USV Laboratories, Division of USV Pharmaceutical Corporation (NDA's 17–126 and 17–127) and approved by the United States Food and Drug Administration.

2. Phenformin is indicated only for symptomatic, adult onset, nonketotic diabetes mellitus (diabetes) (B–506(n)). According to its labeling, phenformin lowers elevated blood glucose levels in diabetics.

3. Phenformin is recommended for use only if diet and weight reduction have first been tried and have failed and only when insulin cannot be used and the sulfonylurea drugs do not achieve adequate control. *Id.*

4. Diabetes is a chronic metabolic disorder in which there is an inadequate secretion or utilization of insulin for normal metabolism (B–497 at 1, B–487 at 12–14, Tr. 92). Diabetes is characterized by an abnormal elevation in blood sugar, which has been used as a principal benchmark in its diagnosis and treatment (B–497 at 2, 8–9, Tr. 87–88, 294).

5. Diabetes is frequently accompanied by severe complications, most particularly cardiovascular and kidney diseases (Tr. 106–107, 295, B–497 at 9–10, CG–43 at 7). Diabetes is the fifth leading cause of death in the United States (CG–43 at 7).

6. There are approximately 5 million diagnosed diabetics in the United States today, most of whom are under treatment (CG–43). About 8 to 12% of these persons were taking phenformin during 1975–1976 (CG–43, CG–20 at 2, CG–11 at 2). The number of persons being treated with phenformin declined from 481,000 in 1974 to approximately 337,000 in 1977 (CG–43, CG–80).

7. The great majority (80–90%) of adult-onset diabetics are overweight (Tr. 406, CG–9 at 2, CG–11 at 2).

8. Dietary control is the most preferred and most effective means for treating adult onset diabetes (B–506(n), B–469 at 3, B–473 at 5, B–499 at 19–20, B–495 at 7, CG–2 at 2, CG–11 at 3). Dietary regulation is the treatment of choice because, when a diabetic's caloric intake is decreased, there is less stress on the available insulin supply, insulin sensitivity is improved (Tr. 11, 94), and the ability to utilize naturally produced insulin is enhanced (B–495 at 10, B–487 at 14–15).

9. The use of exogenous (not produced naturally in the body) insulin is effective in the treatment of adult-onset diabetes by rectifying the insulin deficiency. (B–479 at 17, B–475 at 7). There is evidence that the administration of exogenous insulin also retards the vascular complications of diabetes (Tr. 24, 292–296, B–487 at 12).

10. Phenformin is effective in lowering blood sugar, but this effect is frequently limited to two years or less (Tr. 200–201, 296–297, 303–310, B–475 at 8–9, B–473 at 6, B–489 at 26, B–469 at 9, 13–14, 31). Moreover, the apparent effectiveness is difficult to measure and verify because phenformin is often used in combination with diet and/or sulfonylurea drugs (Tr. 167, 408, 426, 479–483, 523, B–499 at 4, CG–61, CG–20 at 2, CG–15 at 1–2).

11. Phenformin does not stimulate insulin production (B–506(n)). Phenformin does not promote the use of naturally produced insulin (B–495 at 10, Tr. 278–280). Phenformin does not aid or correct the metabolic abnormalities of diabetes (Tr. 295–297, B–497 at 4–5, B–487 at 12–14, B–499 at 20–21). Phenformin does not correct the complications of diabetes (Tr. 443–451, B–344 at 1060). Phenformin does not promote weight reduction (Tr. 450–451, B–509 at 4, 11, B–503 at 6–7, B–475 at 13, B–487 at 16–19, B–72 at 642, B–396 at 105, B–497 at 4).

12. There are essentially no adverse effects involved in the treatment of diabetes by diet and weight reduction. The adverse effects of insulin are far outweighed by its beneficial effects (Tr. 20–21, 198–199, 292–293, 410–411, B–177 at 1, B–475 at 7).

13. Some diabetologists experience difficulty in achieving patient compliance with diet and/or insulin therapies. These problems can be and usually are overcome by diabetologists (Tr. 20–21, 199–200, CG–2 at 2, B–465 at 2–8, 13, B–469 at 3–4, B–503 at 4, B–497 at 24–25).

14. Lactic acidosis is a disorder of intermediary metabolism, in which there is an abnormal accumulation of lactic acid in the blood and tissues (B–489 at 5, B–412 at 40, Tr. 261–262).

15. The fatality rate among persons who suffer from lactic acidosis is

approximately 50% (CG–26, Tables 4 and 5, B–94).

16. Diabetes does not itself cause lactic acidosis (Tr. 262–263, 270, B–499 at 6–10, 17–20, B–475 at 15–17, B–184, B–412 at 50, B–467 at 7–10).

17. A biochemical basis supports the relationship between phenformin and the under utilization and over production of lactate, and the evidence of the modes of phenformin activity provides a probable explanation for this relationship (Tr. 266, 269–277, 461–462, 633–636, B–274, B–68 at 186, B–501 at 2–6, CG–24 at 12, 23, B–487 at 10–11, 16–19, B–497 at 18–23, B–499 at 10–15). The relationship is also supported by the frequently short time between the ingestion of phenformin and the onset of lactic acidosis (B–63 at 44, B–479 at 12–14. B–272 at 70–72, B–487 at 10–11, B–412 at 180).

18. There is a disproportionate incidence of lactic acidosis among diabetics taking phenformin (Tr. 47, 276, B–465 at 11–12, B–473 at 6–9, B–475 at 11–12, 15–17, B–499 at 5–10, 17–18, B–467 at 7–10, B–503 at 10, B–509 at 3, B–479 at 6–10, B–485 at 10, B–64, B–471 at 2, 7–9, CG–20 at 4).

19. Reports in the published medical literature and in retrospective studies constitutes substantial and convincing evidence of the association between lactic acidosis and phenformin, when used alone or in combination with the sulfonylurea drugs (B–64, B–65, B–471, B–290, B–94, B–493 at 3–10, B–92, B–93, B–235, B–236, B–338, B–390, B–33, B–42, B–15, B–96, B–272, B–473 at 6–9, B–475 at 15–18, B–467 at 8–13, B–479 at 3–11, Tr. 634).

20. The association between phenformin and lactic acidosis appears to be dose-related (B–509 at 2–4, B–59, CG–26, Tables 6 and 7, B–481 at 29–30, B–495 at 5, B–64, B–471 at 12–17, B–479 at 11–13, B–63). The association is also supported by evidence involving suicide attempts by use of phenformin (B–479 at 11–14, B–63 at 43–44).

21. An association between phenformin and lactic acidosis need not be based upon quantification of the background incidence of lactic acidosis among the population at large or among the diabetic population not taking phenformin. The background occurrence or incidence is unknown for the vast majority of nonreportable diseases (Tr. 218–219, 363–366, 493–494).

22. A precautionary warning about the possible association between lactic acidosis and phenformin was added by USV to the phenformin labeling in 1964 (CG–25 at 1–2, B–506(e)). A strengthened lactic acidosis warning and statement of contraindications, designed to screen diabetic patients predisposed to lactic acidosis, were added to the labeling in 1970 (CG–25 at 3). In 1974, the lactic acidosis warning was strengthened and a more detailed description of medical conditions predisposing patients to lactic acidosis was included (CG–25 at 7, B–506(k)). A black box warning concerning lactic acidosis was included in phenformin labeling approved June 1976 (CG–25 at 7–8, B–506(m)).

23. The 1970–1976 labeling did not result in limiting the use of phenformin to those patients for whom it was not contraindicated (CG–26, CG–25 at paras. 24, 25, 28 and Exs. 2 and AA, CCD–5, CG–61, CG–63 at 19–20, CG–20 at 2–4, Tr. 348, 357, 383, compare Tr. 555–560 with B–24 at 102 and B–23 at 339, CG–49 at 3).

24. The current (January 1977) labeling for phenformin (B–506(n), Ex. V to CG–25) is designed to restrict its use to only those patients with none of the lactic acidosis predisposing risk factors.

25. The current labeling cannot reasonably be expected to result in the detection of those persons for whom phenformin is contraindicated:

a. With respect to screening for predisposing renal dysfunction, the recommended tests are inadequate and are frequently not performed by general practitioners (B–503 at 12–13, B–495 at 4, B–497 at 4–5, B–487 at 20–22, B–483 at 7–10, B–467 at 11–13, B–489 at 11–14, Tr. 112–116, 592–594).

b. With respect to screening for predisposing liver disease, routine workup is inadequate (Tr. 29–32, 112–121). Thus, compliance with the labeling requirements by general practitioners is unlikely to prevent the occurrence of lactic acidosis (B–471 at 29–30, B–467 at 8–11, 17–18).

26. Lactic acidosis is associated with the use of phenformin even in compliance with the Janurary 1977 labeling, that is, at or below 100 mgs. daily dose and without predisposing risk factors (CG–26, Table 6, B–59 at 4–8, 14–15, and Table 3, B–481 at 29–30, B–495 at 4, B–412 at 180–185, B–272 at 70–72, B–96 at 974–975, B–471 at 2–7, 13–14, 20–31, B–467 at 4–13, 18–19, B–236, B–94, B–493 at 4–13, B–64, Tr. 359–360).

27. The Ciba-Geigy study of the cases of confirmed lactic acidosis associated with phenformin (CG–26) is deficient, and the incidence of lactic acidosis suggested by the data in that study is unreliably low.

a. The study included only those reports in the United States medical literature, whereas several of the retrospective studies are reported in the foreign medical literature (e.g., B–63, B–275, B–276, B–412). Moreover, occurrences of lactic acidosis are likely to be underreported due to a loss of interest in the medical community once a significant number of such reports have been published (B–475 at 12).

b. Physicians are under no legal obligation to report adverse reactions to drug firms. Voluntary reporting, upon which the study is based, significantly understates the true number of adverse reactions (B–479 at 11, B–481 at 8–11, CG–1 at 6, Tr. 43, 336–339, 342–345, 492–505). In measuring adverse reactions, retrospective and prospective patient record reviews, while not ideal, are entitled to greater weight than voluntary reporting to manufacturers (B–481 at 11–14, Tr. 342–345; compare B–479 at 2–11 with Tr. 564–566).

c. The study excluded those cases where there were data indicating impaired renal function. Although impaired renal function is a predisposing factor, those responsible for the study did not determine whether the impaired renal function preexisted use of phenformin or appeared as a consequence of the phenformin-associated lactic acidosis. Thus, exclusion of these data was unjustified. (Tr. 552, 568, 592–594, CG–26 at 5–6, B–475 at 14–15, B–483 at 10–12, B–467 at 11–13, B–493 at 4–8, B–471 at 21–32).

d. The study excluded cases where the data were inadequate to determine the presence of predisposing factors; no attempt to obtain such information was documented in the record (CG–26 at 9).

e. The criteria used in the study to determine the presence of lactic acidosis were more conservative than those used by most investigators (CG–49 at 3, B–471 at 1–5).

28. The reported decrease in the incidence of phenformin-associated lactic acidosis during 1974–1977 must be discounted due to underreporting, a corresponding decrease in the number of diabetics taking phenformin from 481,000 in 1974 to 337,000 in 1977, and a reporting lag time of approximately 9 months (printout attached to CG–26; see Ciba-Geigy/USV Proposed Findings of Fact, para. 22b; Tr. 623–625).

29. Most diabetics in this country who are treated for diabetes by a physician are not treated by a diabetologist (B–483 at 10, B–471 at 23, B–499 at 18–20, Tr. 116–117).

30. The evidence strongly suggests that the incidence of lactic acidosis is greater among patients of general practitioners than among patients of diabetologists (B–477 at 5, B–493 at 4, CG–2 at 4, CG–12 at 9, CG–14 at 2, CG–10 at 3, B–471 at 23, B–499 at 18–20, Tr. 116–119, 347–348, 383, 425–430, 516–524).

31. The testimony of diabetologists about the absence of lactic acidosis among their patients is evidence that the great majority of phenformin-associated lactic acidosis occurs among patients of those physicians with the least special training in screening and testing patients for use of phenformin and in recognizing the consequent lactic acidosis. *Id.* In addition, a significant number of cases of lactic acidosis could exist among the patients treated by diabetologists and general practitioners in the course of their individual practice and be undetected due to their relative infrequency. See Tr. 298–300; *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973).

32. Phenformin has not been shown to be uniquely useful in treating the obese adult-onset diabetic who is "hyperinsulinemic" (B–497 at 5–13 and 25–26, B–509 at 10–11, B–362 at 363–367, B–475 at 18–19, B–503 at 3–4, and B–495 at 9–10, B–469 at 11–13).

33. The removal of phenformin from the market will not seriously disrupt treatment of diabetic patients (CG–10 at 4, B–509 at 3–4, B–467 at 19, B–465 at 4–5, 9–10, B–469 at 8–9, B–479 at 17–19, B–495 at 6–7, B–503 at 7, 14, B–499 at 18–20, B–471 at 22–23, 32, Tr. 298–300).

B. Conclusions of Law.

1. The Bureau of Drugs has sustained its burden of showing, based on new evidence of clinical experience, evaluated together with the data available when the NDA's for phenformin were approved, that phenformin is not shown to be safe for use under the conditions approved in its new drug applications.

2. The Bureau of Drugs has established an association between lactic acidosis and phenformin. Although this relationship has not been conclusively shown to be causal, there is a substantially disproportionate incidence of lactic acidosis among diabetics treated with phenformin.

3. Lactic acidosis is associated with phenformin at dosage levels at or below those prescribed in the January 1977 labeling. Lactic acidosis is associated with phenformin absent the "predisposing factors" for which phenformin is contraindicated.

4. It has not been shown that the current labeling contraindications will reduce the incidence of phenformin-associated lactic acidosis so as to render phenformin safe for use.

5. The risks of the use of phenformin outweigh its benefits.

V. *Final Order*

Therefore, on the basis of the foregoing Findings of Fact and Conclusions of Law, the Initial Decision of the Administrative Law Judge, as modified by this order, and the record of the proceedings, and under the Federal Food, Drug, and Cosmetic Act (sec. 505(e)(2), 52 Stat. 1052 as amended (21 U.S.C. 355(e)(2))) and the authority delegated to the Commissioner (21 CFR 5.1), the new drug applications for phenformin, and all the amendments and supplements thereto, are hereby withdrawn, effective November 15, 1978. The introduction or delivery for introduction into interstate commerce of phenformin, except pursuant to an exemption granted under section 505(i) of the act, is prohibited. 21 U.S.C. 331(d).

Dated: November 15, 1978.

Donald Kennedy,

Commissioner of Food and Drugs.

[Docket No. 77N–0150]

[FR Doc. 79–10593 Filed 4–5–79; 8:45 am]

BILLING CODE 4110–03–M

Phenformin Hydrochloride; Proposal to Withdraw Approval of New Drug Applications; Initial Decision

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency is issuing the Administrative Law Judge's Initial Decision on the proposal to withdraw approval of new drug applications for phenformin hydrochloride.

ADDRESS: The Initial Decision may be seen in the office of the Hearing Clerk (HFA–305), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Richard A. Anderson, Office of the Associate Commissioner for Health Affairs (HYF–21), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1170.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the **Federal Register,** the agency is publishing the Commissioner's final decision on withdrawal of approval of new drug applications for phenformin hydrochloride and his denial of a petition for reconsideration. The Administrative Law Judge's Initial Decision on phenformin hydrochloride is set forth below:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

Initial Decision [1]

[Docket No. 77N–0150]

Proposal to Withdraw Approval of the New Drug Applications for Phenformin Hydrochloride

1. Phenformin found to have limited short-term beneficial effects in the treatment of diabetics under the conditions of use prescribed, recommended or suggested in its labeling.

2. The conditions of use prescribed, recommended or suggested in the labeling for phenformin found inadequate to exclude from treatment those persons for whom the drug is contraindicated as a result of factors which predispose patients to lactic acidosis.

3. The occurrence of lactic acidosis found associated with the use of phenformin in patients for whom the drug is indicated under its current labeling and the incidence of such occurrences as compared to the diabetic population at large is not susceptible of quantification on this record.

4. Therapeutic modalities other than phenformin found shown to be effective for treating patients for whom phenformin is indicated in its labeling without the same degree of risk associated with the use of phenformin.

5. The limited benefits of phenformin found insufficient to support a finding of safety in light of the risks attending its general marketing under the approved NDA's. Approval of the NDA's for phenformin ordered withdrawn pursuant to § 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e).

William Bickerstaff, George Doherty, Richard Morey, Richard Nolan, Richard Serbin, Alfred Schretter, Nicholas Weiskopf, for the manufacturing parties.

Neil Chayet, Michael Morrell, Anthony Roccograndi, and *Daniel Shaw* for the Committee for the Care of the Diabetic.

Arnold Friede, Frederick Degnan, for the Bureau of Drugs, Food and Drug Administration.

By DANIEL J. DAVIDSON, Administrative Law Judge

By notice published in the **Federal Register** of August 12, 1977 (42 FR 40959), this matter was assigned for formal evidentiary public hearing by

[1] Pursuant to § 12.125(a) (21 CFR 12.125(a)), exceptions to this initial decision must be received by the Hearing Clerk not more than 30 days after the date hereof. Replies to exceptions must be received by the Hearing Clerk not more than 20 days thereafter.

order of the Commissioner of Food and Drugs on factual issues relating to the Bureau of Drugs proposed withdrawal of approval of four new drug applications (NDA's) and all NDA amendments and supplements for phenformin hydrochloride. A prehearing conference was held on August 30, 1977. The hearing began on October 5, 1977 and concluded on October 7, 1977. The parties appearing in opposition to the proposed withdrawal were Ciba-Geigy Corporation (herein after referred to as Ciba-Geigy or CG) and USV Pharmaceutical Corporation hereinafter referred to as USV), manufacturers in this proceeding. The Committee for the Care of the Diabetic (CCD) appeared in opposition as a nonparty participant. The Bureau of Drugs of the Food and Drug Administration appeared in support of the proposed withdrawal. Briefs were filed by the Bureau of Drugs, CCD, and jointly by Ciba-Geigy and USV.

History

The New Drug Application (NDA 11–624) for phenformin was approved in 1959 under Section 505 of the Federal Food, Drug, and Cosmetic Act. Three other NDA's (NDA 12–752 in 1961, 17–126 in 1972, and NDA 17–127 in 1972) for phenformin were subsequently approved. In the early sixties, reports of lactic acidosis associated with the drug began to appear. In response to these reports, labeling changes listing contraindications appeared in 1964 and continued until January 1977.

In January 1973, the Bureau of Drugs' Endocrinology and Metabolism Advisory Committee reviewed the problem of phenformin-associated lactic acidosis. The Committee concluded that for patients without predisposing conditions the benefit/risk ration of phenformin was adequate (42 FR 23173). In October 1976, the Committee met again on the same problem and unanimously recommended removal of the drug, but no final determination was made in response to this recommendation (42 FR 23172).

On April 22, 1977, the Secretary of Health, Education and Welfare received a petition from the Health Research Group, a consumer advisory group, requesting that he immediately suspend approval of the new drug applications for phenformin under Section 505(e) of the Federal Food, Drug, and Cosmetic Act on the grounds that the continued marketing of the drug represented an imminent hazard to the public health (42 FR 21845).

A notice was published in the **Federal Register** on April 29, 1977 (42 FR 21845) announcing that a public hearing was to be held May 13, 1977 to receive information and views from interested persons on the issue of whether phenformin, as currently labeled, constitutes such a serious hazard that Section 505(e) of the Act should be invoked to remove the drug from the market.

On May 6, 1977, the Bureau of Drugs commenced formal proceedings to withdraw approval of the phenformin NDA's and all amendments and supplements. An opportunity for hearing on the proposal to withdraw the NDA's was given to all interested persons (42 FR 23170).

After the May 13, 1977 hearing, and upon receiving and reviewing the Commissioner's recommendations, the Secretary, on July 25, 1977, suspended approval of the NDA's for phenformin until completion of administrative proceedings on the withdrawal of these applications (Docket No. 77N–0150) or until termination of these proceedings upon other appropriate action (42 FR 40959). The formal evidentiary public hearing ensued.

Preliminary Matters

Burden of Proof

Under § 505(e)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e)(2),[2] the withdrawal of approval of an NDA requires the Bureau to bear the initial burden of adducing new evidence of clinical experience, which when evaluated along with evidence considered at the time of NDA approval shows that such drug is not shown to be safe for use. See the Circuit Court of Appeals decision in *Hess & Clark* v. *FDA*, 495 F.2d 975, 992 (D.C. Cir. 1974), which dealt with the construction of a virtually identical withdrawal provision in 512(e)(1)(B) (21 U.S.C. 360b(e)(1)(B)). Once this threshold burden is met, the manufacturers would be required to prove the safety of the drug.

The manufacturers contend that the Bureau has failed to sustain its burden of proof to demonstrate "new evidence of clinical experience" because the term "application" as used in § 505(e)(2) applies to the New Drug Application, as of the date of the last supplemental New Drug Application approved by the FDA. In this instance, that would be the supplemental NDA approved by the FDA in January, 1977.

The Bureau asserts that the supplemental NDA approved in 1977 was restrictive in nature (limiting dosage and patient population) and was only approved as an interim measure pending institution of the proceeding seeking total withdrawal.[3] It is further argued that the limiting "new evidence" only to those facts occurring after the date of the approval of the last supplemental application would make the Bureau reluctant to approve future supplemental NDA's on suspect drugs, thereby exposing the public to even greater risk pending the decision to seek total withdrawal of approval. The question of whether the term "application" refers to all of the available data as of the date of the last supplemental NDA or only as of the date of the original application (as is argued by the Bureau is important for determining what clinical evidence will qualify as "new" under the requirement of § 505(e)(2). If the manufacturers' contention is correct, failing the production of significant new evidence subsequent to January 1977, the evidence in this proceeding would have to be considered in light of § 505(e)(1) which requires that the Bureau bear the burden of establishing that the drug is unsafe before an approval of an NDA may be withdrawn.

The statutory burden is different for each section. Under § 505(e)(2), the requirement of showing "that such drug is not shown to be safe for use" means that the Bureau need only raise significant doubts as to the appropriateness of the finding of a prior showing of safety in light of the new evidence. However, the burden under § 505(e)(1) would require the Bureau to introduce evidence establishing that such drug is unsafe for use, thereby justifying withdrawal of the approval of the NDA.

There is no requirement that supplemental NDA's include a resubmission of the same data found in the original NDA. This is evident from the Code of Federal Regulations which indicates that a supplemental application may omit statements made

[2] Section 355(e)(1) and (2) read as follows: The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.

[3] However, this fact was only made known in a speech given by a Bureau official, and was not formerly incorporated in the approval of the supplemental NDA.

in the approved application concerning which no change is proposed (21 CFR 314.8).

The term "application" obviously includes the original application as well as all supplements thereto. However, this does mean that approval of a supplemental NDA grants some type of automatic reaffirmation of all the data used to support the original application, unlimited by the nature of the supplemental change proposed. In the case of phenformin, it is not apparent from a review of the official record of supplemental NDA's that the manufacturers submitted any material other than that relating specifically to the changes sought in connection with each supplemental NDA.

The original studies that provided the basis for the approval of the NDA's for phenformin covered a broad segment of the diabetic population afflicted with maturity onset diabetes mellitus. As experience from resultant human usage became available after approval of the NDA's, the data was used to reevaluate only those areas of the original approval which pertained to the new data. There is no indication that the remaining supportive data for the original studies, for which there was no new data submitted, was entirely reevaluated in connection with any particular supplemental NDA. To the extent that the supplemental NDA's were restrictive in nature, and relied on the supportive data of the original NDA's along with new information, the approval of supplemental NDA's constitutes only limiting amendments of the original NDA's. Under these circumstances, the "new evidence" referred to in § 505(e)(2) cannot reasonably be construed as only that evidence which came to light subsequent to the date of the approval of the most recent supplemental NDA.

Numerous supplemental NDA's for phenformin have been filed and approved since 1959 when the original NDA was approved. Certain of these supplements were filed because newly available evidence gave rise to concerns requiring the modifications sought in the supplemental NDA's. Under these circumstances, the Bureau should not now be precluded from utilizing such evidence for evaluation, along with the data which was available when the original NDA was approved, to support its contention that the drug has not been shown to be safe under the terms of § 505(e)(2).

Motions Renewed on Brief

CCD, in its brief, renews its motion to strike all evidence from the University Group Diabetes Program (UGDP) study because of the Bureau's failure to produce all of the underlying data for said study as required by 21 CFR 12.85. In the alternative, CCD asserts that no weight can be given to such evidence (CCD Brief at 4). Access to underlying data affords an opportunity to evaluate the study's reliability and the validity of the conclusions reached therein.

Although certain underlying data was made available during the hearing, it was admittedly incomplete. The lack of availability of underlying data casts considerable doubt on the reliability of the UGDP conclusions from an evidentiary standpoint. To the extent such data was not made available the UGDP conclusions cannot be considered as substantiated on this record. However, no specific analysis of said data was submitted to show the precise extent to which the UGDP data was unsupported, and therefore, which specific portions of the UGDP data should be stricken on that basis.

In such circumstances, it appears that the UGDP conclusions may form the basis for expert opinion testimony and may properly be considered for the purpose of raising questions as to the safety of phenformin. This is particularly true when the UGDP is considered along with the other evidence of record requiring similar conclusions. Accordingly, the prior ruling denying CCD's motion to strike all of the UGDP data is affirmed.

CCD also contends that the foreign clinical data relied upon by the Bureau violates 21 CFR 312.20 (CCD Brief at 35) and so cannot be admitted as evidence. CCD further asserts that the foreign studies failed to define cases " * * * in which lactic acidosis occurred in the absence of other conditions producing lactic acidosis, or to determine whether the administration of phenformin was to patients in whom the medication was *not* contraindicated" (CCD Brief at 28). The regulation cited deals with the requirements for clinical data necessary to support a finding of safety and effectiveness before a new drug application may be approved. This is an altogether different situation than where foreign clinical data is considered because it raises questions as to the safety of a drug. Valid data and information from a technically incomplete study may nevertheless establish the presence of a previously unsuspected hazard thereby requiring further investigation to resolve the question of safety. Although the foreign clinical data would not qualify to the extent necessary to support a *prima facie* finding, it may nevertheless be considered as part of the overall body of available safety data.

Positions of Participants

The manufacturers and CCD assert that phenformin is highly and often uniquely beneficial in the treatment of diabetic patients for whom the drug is indicated by the current labeling. This labeling is deemed by them to exclude from treatment diabetic patients predisposed to lactic acidosis. It is further asserted that the Bureau has failed to sustain its burden of proof to demonstrate adequate new evidence that phenformin is not safe. Therefore, the manufacturers and CCD believe that phenformin should enjoy continued marketing under the current labeling.

The Bureau believes that its burden in this cast is to demonstrate an association between phenformin and lactic acidosis while the opponents of the withdrawal must prove its safety. The Bureau asserts that phenformin is of no benefit in the treatment of diabetes, and that it produces lactic acidosis even in the face of label warnings. Considering the danger and lack of efficacy of phenformin, the Bureau believes it should remain off the market.

For procedural purposes, the participation of USV at the oral hearing was grouped with that of Ciba-Geigy because their interests in the present proceeding are nearly identical. USV did not offer evidence through any separate witness and filed its post-hearing brief jointly with Ciba-Geigy. Therefore, reference to arguments or allegations in this decision may refer to USV and Ciba-Geigy jointly.

CCD contends that its "interests have not been fully protected since it has been denied full party status" in the present proceeding (CCD Brief at 2). As CCD did not exercise the right to request a formal evidentiary hearing in this matter, its status in the present proceeding is limited to that of a participant (21 CFR 10.1(a)(10)). Although CCD's initial request for involvement in the hearing was untimely made, it was nevertheless granted the right of participation pursuant to § 12.45(f) (21 CFR 12.45(f)), (Prehearing Transcript, August 30, 1977 at 36). At the time of the granting of nonparty participant status, CCD's representative was instructed as to the opportunity for enlargement of their rights under § 12.89(d) (21 CFR 12.89(d)). While CCD was provided ample opportunity to seek additional rights, no specific showing sufficient to justify the granting of such additional rights was ever made. Therefore, CCD's rights were properly limited under the provisions of § 12.89(d)

to that of nonparty participant, and the assertion that their interests have not been fully protected is without merit.

Basic Mechanisms of Phenformin Activity

There have been many submissions to the record concerning the scientific research which has served to clarify and define the mechanisms involved in the production of the biological consequences of phenformin therapy. Ciba-Geigy and USV believe that the Bureau must show that there exists "a plausible biomedical explanation as to why such elevations [of blood lactate levels] occur," before phenformin may be found unsafe (CG Brief 34). The statutory basis for such a requirement is unclear and no authority is cited to support this assertion.

Evidence of clearly defined mechanisms of action is not required to prove the efficacy of a drug. Since the absence of a scientific hypothesis to explain how or why a drug acts does not preclude consideration of observed therapeutic effects, it should similarly not be expected to preclude consideration of any deleterious effects.

In any event, there is substantial evidence relating to mechanisms of action of phenformin. There has been testimony to the effect that one of the actions of phenformin is to decrease intestinal glucose absorption. Dr. Williams (Ex. No. B–497) noted in an editorial (Ex. No. B–269) that the reseacher, Czyzyk, showed that phenformin was ineffective in lowering glucose levels when the sugar was administered intraveneously, but that it became effective when it was given orally (Ex. No. B–69 at 492). This phenomenon was accounted for by the hypothesized role of the drug in suppressing glucose absorption from the gastrointestinal tract. (Ex. No. B–497 at 17). Dr. Felig found support for this explanation of phenformin activity in Dr. Cash's testimony (Tr. 285, citing Ex. No. CG–24 at 19). Ciba-Geigy witness Dr. Levine apparently agrees, testifying that, "There is lessened absorption of glucose, some amino acids, and other materials" with the use of phenformin (Tr. 458).

There is also evidence to the effect that phenformin cause an increase in blood lactate levels and in the blood lactate/pyruvate ratio (Tr. 270). Dr. Alberti testified that his basic research demonstrated that in patients receiving a dosage of 100 mg per day of phenformin (Ex. No. B–487 at 18) the mean blood lactate levels were grossly elevated, and the lactate/pyruvate ratio was increased (Ex. No. B–274). Dr. Miller, although employing dosages ranging from 150–175 milligrams which are higher than those in the aforementioned study (Ex. No. B–68 at 186), reported a similar increase in both the fasting blood lactic acid concentration and the blood lactate/pyruvate ratio (Ex. No. B–501 at 2–3. Interestingly, even at a dose of 50 mg a day, half the amount suggested by phenformin labeling, there is still a demonstraton of increased blood lactate levels (Ex. No. 501 at 6). Dr. Felig points out that due to differences in metabolic processes, diabetics demonstrate an increased trunover rate of lactate as compared to that of the general public, allowing diabetics to utilize lactate more rapidly than nondiabetics. Therefore, it is unlikely, absent other factors, that diabetics would show high or even average lactate levels (Tr. 263). Furthermore, phenformin has induced higher blood lactate levels even in nondiabetics. Therefore, the increased levels cannot be accounted for by the diabetic state alone (Ex. No. B–487 at 23). Elevated plasma levels of phenformin have been associated with lactic acidosis (Ex. No. B–489 at 11), although this increase does not appear to be a prerequisite to phenformin induction of lactic acidosis (Ex. No. B–497 at 21).

The effect of phenformin in increasing lactate and pyruvate production has been affirmed by Dr. Levine (Tr. 462). Dr. Cash also admits the drug has a hyperlactacidemic effect, although he terms it mild (Ex. No. CG–24 at 12) and dose-related (Ex. No. CG–24 at 23). Exacerbating the increase of blood lactate levels is the drug's ability to decrease the acid excretion rate by 50% in pastients taking 50 milligrams of phenformin daily (Ex. No. B–471 at 11), and its effect of impairing the removal of lactate from the blood by the liver (Ex. No. B–471 at 29).

Ciba-Geigy and USV assert that one of the Bureau's contentions is "that phenformin causes a shortage of oxygen (tissue hypoxia) which yields an anaerobic metabolic state * * *" (CG–USV Proposed Findings of Fact at 48). Ciba-Geigy witnesses have testified that quanadines inhibit oxygen uptake at high levels, but feel that this effect does not demonstrate itself at the therapeutic levels of the drug (Tr. 454 and 467). However, as this property of oxygen uptake inhibition does appear to be within the capacity of this family of chemicals, it does not appear unreasonable to suspect that the effect may continue at a lower level below the sensitivity of the detection method. Furthermore, as many of the acidosis cases are reported in patients who have a decrease in the ability to eliminate the drug from their system, amounts of phenformin above therapeutic levels may be reached in their bloodstreams through accumulation despite the limitation of the oral administration of phenformin to the levels indicated in the labeling. The assumption by Ciba-Geigy witnesses that the ability of phenformin to inhibit oxygen uptake will not demonstrate itself when patients ingest 100 mg a day or less does not take into account the case of variations in individual sensitivity to the drug or individuals with heightened susceptibility to side effects which is not diagnoseable prior to administration of the drug. (Ex. No. B–429 at 14).

The Bureau does not limit its theory, however, to a consideration of anoxia. For instance, Bureau witness Dr. Williams, testified that "A decrease in oxygen can mimic the effects of phenformin" (Ex. No. B–497 at 18) showing only that phenformin demonstrates the same influence on metabolism as does oxygen deficiency. The Bureau's hypothesis lies in a conviction that the anaerobic pathway is resorted to when phenformin is administered. Dr. Kreisberg attributes this increased rate of anaerobic glycolysis to an interference with mitachondrial function which can occur despite the presence of oxygen (Ex. No. B–499 at 12). He notes that this mechanism would also tend to increase the lactate to pyruvate ratio. Dr. Tranquada also characterizes the effects of phenformin as causing an increased reliance on the anaerobic pathway of glycolysis (Ex. No. B–467 at 15).

The suppression of oxidative reactions by phenformin has been seen as resulting in a decrease in gluconeogenesis by the research of Dr. Williams (Ex. Nos. B–269 at 18 and B–497). Dr. Levine also testified that phenformin inhibits glyconeogenesis (Tr. 461). Dr. Alberti sees this interference as causing the accumulation of its precursors, pyruvate and lactate, the latter accounting for half of the newly produced glucose (Ex. No. B–487 at 11).

Dr. Kreisberg testified that the animal studies in this area show that phenformin inhibits the synthesis of lactate into glucose by the liver (Ex. No. B–499 at 15). He also notes that this effect would decrease the regeneration of bicarbonate which could otherwise have been used in minimizing the effects of acidosis (Ex. No. B–499 at 16). Dr. Cash on the other hand, states that the only research he deems valid in this area indicates that glucose synthesis is enhanced by phenformin (Ex. No. CG–24

at 16). However, this appears to be a minority view considering the opinions of the other expert witnesses testifying at this proceeding.

While it appears that the mechanisms of phenformin activity have not been definitively established, the results of the scientific investigations in this area are strongly suggestive of possible modes of phenformin's activity. Phenformin inhibits the absorption of glucose and other materials from the intestinal tract. It also is associated with an increase in blood lactate levels and in the lactate/pyruvate ratio. This shift in the lactate/pyruvate ratio is particularly important in terms of gluconeogenesis, as lactate must be converted to pyruvate before it can be utilized in this cycle. Thus, an inhibition of this conversion could lead to a suppression of the gluconeogenic processes. Phenformin causes the cell to shift from aerobic to anaerobic metabolism, a biochemical pathway whose effects would account for many of the influences associated with the administration of phenformin. Glyconeogenesis is also suppressed by phenformin, accounting in part for the inability of the liver to compensate for the elevation in blood lactate levels which result from a shift to anaerobic metabolism.

Although, as in any scientific investigation, the research into the mechanisms or phenformin is not totally definitive, it does provide a probable explanation for the occurrence of lactic acidosis that has been associated with the administration of this drug. The results of this basic research are important to the present determination for several reasons. The manufacturers have noted that above "therapeutic" levels, phenformin causes lactic acidosis. Individual metabolic variation among patients has been demonstrated in some subjects with no renal or liver dysfunction who have high blood levels of phenformin while receiving low to moderate oral doses of this drug (Ex. No. B–501 at 6). On the other hand, some patients, again without detectable predisposing factors, have suffered lactic acidosis even when their blood levels of phenformin have been normal (Ex. No. B–489 at 11). Such evidence demonstrates that physician screening of candidates for this treatment may be insufficient to preclude phenformin administration to patients at risk for the often fatal side effect of lactic acidosis.

Safety Evidence

Ciba-Geigy claims that no scientifically valid conclusions concerning an association between phenformin and lactic acidosis can be drawn by simply aggregating cases of lactic acidosis during phenformin therapy, without reference to (a) existing label restrictions, (b) the background occurrence of lactic acidosis in the patient population in question, or (c) the various bias factors typically accompanying retrospective (or even prospective) searches for an adverse reation (Ex. No. CG Brief at 27).

As will be further discussed in the section on *Inability to Comply With Label Requirements*, it is unreasonable, in the case of phenformin, to limit consideration of adverse effects only to those instances of strict compliance with the conditions of use prescribed, recommended or suggested in the labeling. Under the labeling restrictions, maximum daily recommended dosages of 300 milligrams, 200 milligrams, and 100 milligrams have not precluded the continuing appearance of lactic acidosis. In fact, there appears to be a correlation between dosage and the occurrence of lactic acidosis.

Dr. Stolley testified that the background occurrence or incidence in the general population is unknow for 99 percent of the nonreportable diseases, lactic acidosis being no exception to this trend (Tr. 365). The background occurrence for drawing an association between phenformin and lactic acidosis in not necessary as evidenced by Ciba-Geigy witness Dr. Schoenberger who stated that all he would need to evaluate whether the incidence of lactic acidosis in patients who had taken phenformin was too high would be "* * * the number of cases that occur in a given period of time among the individuals who take the drug" (Tr. 493–494). Because there is a lack of a base rate for most illnesses, the lack of an absolute base rate for lactic acidosis should not preclude the finding that lactic acidosis in phenformin users is associated with the use of the drug.

Admittedly, there is always bias in any given study. The difficulty comes in measuring that degree of bias. Dr. Danowski, a Ciba-Geigy witness, suggests that in order for bias not to enter into the collection of data "* * * there should have been first independent searches for lactic acidosis without regard to diagnosis in therapy and for lactic acidosis in diabetes mellitus without and with DBI or other drug treatment" (Ex. No. CG–4 at 6). Yet Ciba-Geigy's review of lactic acidosis cases beginning with suspected lactic acidosis during phenformin therapy does not meet the above standard. On the other hand, the studies of Dr. Tranquada, Dr. Fulop and Dr. Brach, *et al.* do meet this Ciba-Geigy criteria for mitigating bias factors. As for the remaining studies, either it could not be determined from the record whether Ciba-Geigy's bias standard had been followed or such a standard was not met. However, this does not mean that such studies may not be considered for the purpose of raising questions as to the safety of phenformin and as corroboration for similar conclusions reached in the other studies.

A flawless human test designed to determine the rate of a drug's side effect which demonstrates a high morbidity and mortality rate is unlikely to occur because the morality of such a method is questionable. The UGDP study is an example of this problem. When potentially lethal side effects were seen in the phenformin group, it became unconscionable to allow continued patient usage for the purpose of scientific study.

As stated in the testimony of Dr. Felts (Ex. No. B–477 at 6):

> I have reviewed the literature and it is difficult to find absolutely unequivocal cause-and-effect relationships. But I think that our search to try to find this unequivocal relationship has resulted in a lot of people dying as a result of lactic acidosis because phenformin is still available.Q04

Therefore, it is improper to hold human studies to the same requirements as animal experiments because the deaths that would be required in good animal studies cannot be allowed when humans are used as experimental subjects.

Bureau's Evidence

The Bureau maintains that there are sufficient studies available to indicate a positive association between phenformin and lactic acidosis. Dr. Tranquada's study at the Los Angeles County Hospital consisted of 46 patients with lactic acidosis having a blood lactate of 7 millimoles or greater. Twenty-six of the 46 lactate acidosis patients were diabetics with seven on phenformin. Six of the seven patients' daily doses were known to be 50, 75, 100, 100, 150 and 150 milligrams (Ex. No. B–467 at 4–11). At the time of this study, the maximum daily dose recommended by the manufacturers was 300 milligrams or less while the current recommended daily dose is 100 milligrams or less. This would seem to indicate that there is no safe dosage level for phenformin.

Dr. Tranquada had personally encountered nine cases of lactic acidosis in diabetic patients receiving between 50 to 200 milligrams per day who had no other identifiable cause of lactic acidosis. Eight of these nine had

impaired renal function, but it could not be determined if this problem developed prior to lactic acidosis because evidence of renal dysfunction often accompanies lactic acidosis. The three patients who survived lactic acidosis had normal renal function after recovery (Ex. No. B–467 at 11–13).

Dr. Tranquada found that approximately 55 to 60 percent of the diabetic patients with lactic acidosis that he saw had not been receiving phenformin. However, with only 1 percent of diabetics being treated with phenformin, the 40 to 45 percent of the diabetics with lactic acidosis who had been receiving phenformin was too great a number for there not to be an association. (Ex. No. B–467 at 10).

A retrospective study conducted over 17 months by Dr. Loewenstein found six cases of diabetics with lactic acidosis, five of whom were taking phenformin (Ex. No. B–471 at 2). He then conducted a prospective study for the next 18 months in which he found that 6 of 7 diabetics with lactic acidosis were taking phenformin (Ex. No. B–471 at 14). The blood lactate level was 5 millimolar or greater or an unexplained anion gap of 20 milliequivalents per liter (mEg/L). normal persons have an arterial lactate level of 1 or 1.5 millimolar (Ex. No. B–471 at 3–4). Combining these two studies, there were over a 3-year period a total of 13 diabetics with lactic acidosis of which eleven were taking phenformin. Three of these eleven had no other precipitating cause of lactic acidosis although they did have hypertension which is not a label contraindication (Ex. No. B–471 at 20).[4] Sufficient data was available for eight patients to indicate that two were contraindicated under the 1977 labeling but six were not (Ex. No. B–471 at 30). This would seem to indicate that not all patients at risk can be identified. Dr. Loewenstein's studies show that 85 percent of diabetics with lactic acidosis were on phenformin.

Dr. Loewenstein also found additional cases of phenformin-treated patients with lactic acidosis. Of this group, two were taking 50 milligrams daily, two were taking 100 milligrams daily, and the dosage for the remaining two was not indicated. Three of the patients taking phenformin had been on it two weeks or less (Ex. No. B–471 at 31). Dr. Loewenstein's retrospective study showed three of five patients taking 100 milligrams per day, one patient taking 150 milligrams per day, and the dosage for the other patient was not indicated (Ex. No. B–471 at 7).

A retrospective review of patients' records from 1970 to 1972 was conducted at Beth Israel Hospital by Dr. Davidoff. His criteria for determining lactic acidosis was either a total bicarbonate of 13 or less plus a large anion gap, an arterial pH of 7.31 or less, or both. He found seven cases of diabetics with lactic acidosis who had no obvious precipitating causes. All were taking phenformin (Ex. No. B–479 at 5–7).

A two-year prospective study of patients with metabolic acidosis was conducted at the Bronx Municipal Hospital by Dr. Fulop. Eighteen diabetics with lactic acidosis taking phenformin were found. Ten of these 18 had no identifiable disease other than their lactic acidosis (Ex. No. B–493 at 4–6). There was a 50 percent mortality rate with only nine patients surviving. Six of the nine survivors had normal values or serum urea nitrogen before they left the hospital. This indicates that their impaired kidney function was temporary (Ex. No. B–493 at 8). Eight of the 18 took no dose greater than 150 milligrams per day and seven of the eight took no more than 100 milligrams daily. There was no reliable dosage information for the other ten patients. Of the seven who took no more than 100 milligrams, four had no other serious diseases associated with lactic acidosis (Ex. No. B–493 at 13).

A nineteen-month review of 2,647 consecutive deaths whose final diagnosis included "acidosis" was conducted at Charity Hospital, a large metropolitan hospital in New Orleans, by Dr. Brach, *et al.* Only the records of patients with a minimum age of twelve were examined. Metabolic acidosis as a contributory or primary source of death was found in 27 cases. In ten of the 27, a presumptive diagnosis of lactic acidosis could be made. Eight of these 10 cases were diabetic and all were taking phenformin (Ex. No. B–42 at 202–203). Lactic acidosis could be diagnosed with certainty on the basis of determinations of blood lactate concentration in only four cases. The other six lactic acidosis cases were determined by an increased anion gap (Ex. No. B–42 at 204). In two of the eight fatal cases, phenformin had been given despite the contraindication of mild azotemia. One had received phenformin during a postoperative period and two other patients had hypertensive cardiovascular diseases. None of the eight received over 150 milligrams per day (Ex. No. B–42 at 205).

Ciba-Geigy's review of all cases of lactic acidosis reported to it or found in the domestic medical literature revealed 39 cases of phenformin-treated patients with confirmed lactic acidosis for which no known causal, predisposing or contributory conditions or factors could be identified. In addition, 188 phenformin-treated patients were considered to have confirmed lactic acidosis, accompanied by conditions known to have either causal or contributory relationships to the development of lactic acidosis (Ex. No. B–59 at 5). Ciba-Geigy's criteria for confirmed cases of lactic acidosis consisted of a lactate level of 6.5 mEg/L or greater, accompanied by a pH of 7.33 or less (Ex. No. B–59 at 4–5). Lactate levels above 7 to 8 mEg/L are usually associated with a fatal outcome (Ex. No. B–184 at 209).

Information concerning the daily dosage of phenformin at the time of occurrence of lactic acidosis for the years 1974, 1975, and 1976, indicated that the most common daily dosage seen at the outset of lactic acidosis was 100 milligrams (Ex. No. B–59 at 7). Table 3 (Ex. No. B–59 at 14) shows that in 1974, out of a total of 86 cases, 39 were taking 100 milligrams or less, 23 were taking over 100 milligrams, and the dosage for 24 was unknown at the time lactic acidosis occurred. In 1975, 17 were taking 100 milligrams or less, 15 were taking more than 100 milligrams, and in 10, the dosage was unknown out of a total of 42 cases. In 1976, 9 were taking 100 milligrams or less, 9 were taking over 100 milligrams, and the dosage for one case was unknown out of a total of 19 cases. In each of these years, for the known dosages, at least 50 percent or more of the patients who developed lactic acidosis were on the 1977 recommended dosage of 100 milligrams or less.

Concerning those same years, Ciba-Geigy compared daily dosage with the estimated percent of market usage, and stated that "* * * while less than 10% of phenformin usage occurs at dosages over 100 mg per day, dosages in excess of 100 mg daily are associated with approximately 40% of the reported cases of lactic acidosis" (Ex. No. B–59 at 8). This means, conversely, that approximately 60% of the reported cases of lactic acidosis occurred at the recommended dosage of 100 milligrams or less.

There have been serveral documented suicide attempts where people have taken an overdose of phenformin and

[4] Although hypertension is not listed as a contraindication according to the January 1977 label restrictions, it may be associated with various degrees of cardiovascular disease. The label specifically lists "any acute medical situation such as cardiovascular collapse (shock), congestive heart failure [or] acute or suspected myocardial infarction" as contraindications. The label's failure to indicate whether hypertension is considered a cardiovascular disease further points out the difficulty physicians encounter when attempting to follow the label restrictions.

developed lactic acidosis as a direct result (Ex. No. B–479 at 11). Dr. Cohen, *et al.*, reported the case of a previously healthy 17 year old boy who took 1500–2000 mg at 6 p.m. and at 8:30 a.m. the next morning was admitted to the hospital suffering from lactic acidosis (Ex. No. B–63 at 43–44). The researchers concluded that "* * * the close relationship of the time of first administration of Phenformin to the onset of lactic acidosis together with the absence of arterial oxygen desaturation, hypotension, or peripheral vasoconstriction leaves little doubt that Phenformin was directly responsible for the lactic acidosis" (Ex. No. B–63 at 44).

In his testimony, Dr. Davidoff described a published report of a German woman who developed servere lactic acidosis while on phenformin. She was 57, had been taking a daily dosage of 150 mg and had the predisposing factors of cardiac failure an slight renal failure. When admitted to the clinic her lactate levels measures almost 19mEg/L (Ex. No. B–479 at 12–13). After the patient had recovered, she was placed back on phenformin under close supervision, with her blood tests being followed in order to establish whether or not phenformin had been a contributing factor in her lactic acidosis. Over a period of one week on 150 mg per day, her lactate which started at about one mEg/L rose to almost 4 mEg/L. Dr. Davidoff indicated that a rise is very unusual for patients taking phenformin. Therefore, phenformin was discontinued. This patient seemed to be biochemically at risk to excess accumulation of lactate. This case clearly indicate that phenformin was a contributing factor in lactic acidosis (Ex. No. B–479 at 13–14).

The analysis of phenformin dosage in 44 cases by Dr. Cohen, *et al.*, of the time intervals between the start of phenformin therapy, or an increase in dose, and the onset of lactic acidosis showed that 24 out of 34 patients in whom sufficient data was available developed lactic acidosis wihtin 2 months of the start of therapiutic doses. The onset of lactic acidosis occurred within two weeks in 17 patients (Ex. No. B–63 at 44). "If lactic acidosis had resulted purely from longstanding conditions such as cirrhosis or diabetes, such an early concentration of incidence would not have been expected" (Ex. No. B–63 at 44).

The UGDP study was a long-term prospective clinical trial carried out mainly in the sixties. It was designed to determine the effects of hypoglycemic agents on vascular complications in adult-onset diabetes and not to determine the incidence of lactic acidosis in phenformin users (Ex. No. B–396). There were 204 patients randomly assigned to phenformin (Ex. No. B–396 at 67). The daily phenformin dosage was 100 mg (Ex. No. B–396 at 65). In the phenformin-treated group one death was ascribed to lactic acidosis and two cases of nonfatal lactic acidosis were reported (Ex. No. B–396 at 72). The one patient who died of lactic acidosis had cardiovascular and renal disease along with hypertension (Tr. 536). Only renal disease with uremia was contraindicated in the labeling at the time phenformin was prescribed for her [Ex. No. B–506(e)]. No data was available with respect to the two nonfatal cases of lactic acidosis.

Gale and Tattersall conducted a retrospective study at General Hospital, Nottingham, from 1972–1975 and found eight diabetics with lactic acidosis that met their criteria of a blood lactate concentration of over 7 mmol/1 or an anion gap greater than 30 mmol/1 with a negative Acetest reaction on undiluted plasma. All eight lactic acidosis patients were taking phenformin and all died (Ex. No. B–96 at 973). Five patients were taking only 100 mg per day (Ex. No. B–96 at 974). Two patients were contraindicated, four had hypertension and minial evidence of renal disease, and two had no predisposing factors (Ex. No. B–96 at 972). Of the two noncontraindicated patients, one was taking only 100 mg daily, while the dosage of the other one could not be determined from the record. Lactic acidosis developed rapidly with an increased dosage of 200 mg per day after 5 days in 1 patient and after 15 days in another. Still another developed lactic acidosis after only 5 days on 100 mg while 2 others on 100 mg got lactic acidosis within 6 months. The 3 patients on 100 mg developed lactic acidosis 2 to 8 years after starting phenformin.

The Wise and Chapman study found that during a two-year period 38 diabetics with lactic acidosis were admitted to the Royal Adelaide Hospital. The criteria for establishing lactic acidosis was a lactic value of 2 mmol/1 or more and an arterial pH of less than 7.37. Twenty of the 38 patients were on phenformin with 15 having nonketotic or metabolic lactic acidosis. Of these 15 patients, ten received a daily dosage of 100 mg or less alone or in combination with sulphonylureas or insulin. Duration of phenformin treatment ranged from less than a month for five cases, from one month to a year for three cases, and one to ten years for seven cases (Ex. No. B–272 at 70). Seven patients had either started the drug or received a dose increase within the month before the occurrence of lactic acidosis (Ex. No. B–272 at 72). Six of the ten patients receiving 100 mg or less died (Ex. No. B–272 at 71). All but one of the 15 patients had additional renal or cardiovascular abnormalities or both (Ex. No. B–272 at 70).

Dr. Palumbo of the Mayo Clinic stated that he had never personally "* * * seen lactic acidosis in diabetics not treated with phenformin" (Ex. No. B–503 at 10). Dr. Kreisberg testified that:

> It is striking and almost an invariable finding that lactic acidosis in diabetics in our emergency room, in the absence of myocardial infarction and all other things that are known to produce lactic acidosis, is seen within the framework of the use of phenformin (Ex. No. B–499 at 18).

Dr. John Davidson, who sees two or three cases per year of phenformin-associated lactic acidosis at Grady Memorial Hospital in Atlanta, testified that he didn't remember having seen a diabetic with lactic acidosis in the last few years who was not on phenformin therapy (Ex. No. B–465 at 12).

Through the Diabetes Literature Index, Dr. Davidoff totaled the recorded cases of lactic acidosis and said:

> * * * without trying to be exhaustive, I was able to come up, I think in 1975, with something of the order of 104 cases of what appeared to be phenformin-associated lactic acidosis out of about 163 total cases of lactic acidosis in the literature and noted that there had been more since that effort on my part to actually add up the numbers (Ex. No. B–479 at 10).

Dr. Daughaday, who has been alert to the problems of lactic acidosis for at least 15 years, sees 1 to 3 cases of phenformin-associated lactic acidosis a year (Ex. No. B–473 at 11), while Dr. Felts for the last ten years has consulted on one or two cases per year of phenformin-associated lactic acidosis (Ex. No. B–477 at 5–6). Dr. Loewenstein of LSU School of Medicine said that "At our institution, most of the diabetics who have had lactic acidosis, in fact, almost all of the diabetics have been taking phenformin" (Tr. 47). Finally, Dr. Felig of Yale said:

> It should be emphasized that where lactic acidosis has been seen in diabetic patients within the last 10 years, it has been virtually always in association with phenformin administration (Tr. 276).

In all probability the cases in evidence are only a portion of those occurring in the United States. While underestimation will not establish an accurate rate for the incidence of phenformin-associated lactic acidosis, the cases are nevertheless valuable for

impaired renal function, but it could not be determined if this problem developed prior to lactic acidosis because evidence of renal dysfunction often accompanies lactic acidosis. The three patients who survived lactic acidosis had normal renal function after recovery (Ex. No. B–467 at 11–13).

Dr. Tranquada found that approximately 55 to 60 percent of the diabetic patients with lactic acidosis that he saw had not been receiving phenformin. However, with only 1 percent of diabetics being treated with phenformin, the 40 to 45 percent of the diabetics with lactic acidosis who had been receiving phenformin was too great a number for there not to be an association. (Ex. No. B–467 at 10).

A retrospective study conducted over 17 months by Dr. Loewenstein found six cases of diabetics with lactic acidosis, five of whom were taking phenformin (Ex. No. B–471 at 2). He then conducted a prospective study for the next 18 months in which he found that 6 of 7 diabetics with lactic acidosis were taking phenformin (Ex. No. B–471 at 14). The blood lactate level was 5 millimolar or greater or an unexplained anion gap of 20 milliequivalents per liter (mEg/L). normal persons have an arterial lactate level of 1 or 1.5 millimolar (Ex. No. B–471 at 3–4). Combining these two studies, there were over a 3-year period a total of 13 diabetics with lactic acidosis of which eleven were taking phenformin. Three of these eleven had no other precipitating cause of lactic acidosis although they did have hypertension which is not a label contraindication (Ex. No. B–471 at 20).[4] Sufficient data was available for eight patients to indicate that two were contraindicated under the 1977 labeling but six were not (Ex. No. B–471 at 30). This would seem to indicate that not all patients at risk can be identified. Dr. Loewenstein's studies show that 85 percent of diabetics with lactic acidosis were on phenformin.

Dr. Loewenstein also found additional cases of phenformin-treated patients with lactic acidosis. Of this group, two were taking 50 milligrams daily, two were taking 100 milligrams daily, and the dosage for the remaining two was not indicated. Three of the patients taking phenformin had been on it two weeks or less (Ex. No. B–471 at 31). Dr. Loewenstein's retrospective study showed three of five patients taking 100 milligrams per day, one patient taking 150 milligrams per day, and the dosage for the other patient was not indicated (Ex. No. B–471 at 7).

A retrospective review of patients' records from 1970 to 1972 was conducted at Beth Israel Hospital by Dr. Davidoff. His criteria for determining lactic acidosis was either a total bicarbonate of 13 or less plus a large anion gap, an arterial pH of 7.31 or less, or both. He found seven cases of diabetics with lactic acidosis who had no obvious precipitating causes. All were taking phenformin (Ex. No. B–479 at 5–7).

A two-year prospective study of patients with metabolic acidosis was conducted at the Bronx Municipal Hospital by Dr. Fulop. Eighteen diabetics with lactic acidosis taking phenformin were found. Ten of these 18 had no identifiable disease other than their lactic acidosis (Ex. No. B–493 at 4–6). There was a 50 percent mortality rate with only nine patients surviving. Six of the nine survivors had normal values or serum urea nitrogen before they left the hospital. This indicates that their impaired kidney function was temporary (Ex. No. B–493 at 8). Eight of the 18 took no dose greater than 150 milligrams per day and seven of the eight took no more than 100 milligrams daily. There was no reliable dosage information for the other ten patients. Of the seven who took no more than 100 milligrams, four had no other serious diseases associated with lactic acidosis (Ex. No. B–493 at 13).

A nineteen-month review of 2,647 consecutive deaths whose final diagnosis included "acidosis" was conducted at Charity Hospital, a large metropolitan hospital in New Orleans, by Dr. Brach, *et al.* Only the records of patients with a minimum age of twelve were examined. Metabolic acidosis as a contributory or primary source of death was found in 27 cases. In ten of the 27, a presumptive diagnosis of lactic acidosis could be made. Eight of these 10 cases were diabetic and all were taking phenformin (Ex. No. B–42 at 202–203). Lactic acidosis could be diagnosed with certainty on the basis of determinations of blood lactate concentration in only four cases. The other six lactic acidosis cases were determined by an increased anion gap (Ex. No. B–42 at 204). In two of the eight fatal cases, phenformin had been given despite the contraindication of mild azotemia. One had received phenformin during a postoperative period and two other patients had hypertensive cardiovascular diseases. None of the eight received over 150 milligrams per day (Ex. No. B–42 at 205).

Ciba-Geigy's review of all cases of lactic acidosis reported to it or found in the domestic medical literature revealed 39 cases of phenformin-treated patients with confirmed lactic acidosis for which no known causal, predisposing or contributory conditions or factors could be identified. In addition, 188 phenformin-treated patients were considered to have confirmed lactic acidosis, accompanied by conditions known to have either causal or contributory relationships to the development of lactic acidosis (Ex. No. B–59 at 5). Ciba-Geigy's criteria for confirmed cases of lactic acidosis consisted of a lactate level of 6.5 mEg/L or greater, accompanied by a pH of 7.33 or less (Ex. No. B–59 at 4–5). Lactate levels above 7 to 8 mEg/L are usually associated with a fatal outcome (Ex. No. B–184 at 209).

Information concerning the daily dosage of phenformin at the time of occurrence of lactic acidosis for the years 1974, 1975, and 1976, indicated that the most common daily dosage seen at the outset of lactic acidosis was 100 milligrams (Ex. No. B–59 at 7). Table 3 (Ex. No. B–59 at 14) shows that in 1974, out of a total of 86 cases, 39 were taking 100 milligrams or less, 23 were taking over 100 milligrams, and the dosage for 24 was unknown at the time lactic acidosis occurred. In 1975, 17 were taking 100 milligrams or less, 15 were taking more than 100 milligrams, and in 10, the dosage was unknown out of a total of 42 cases. In 1976, 9 were taking 100 milligrams or less, 9 were taking over 100 milligrams, and the dosage for one case was unknown out of a total of 19 cases. In each of these years, for the known dosages, at least 50 percent or more of the patients who developed lactic acidosis were on the 1977 recommended dosage of 100 milligrams or less.

Concerning those same years, Ciba-Geigy compared daily dosage with the estimated percent of market usage, and stated that "* * * while less than 10% of phenformin usage occurs at dosages over 100 mg per day, dosages in excess of 100 mg daily are associated with approximately 40% of the reported cases of lactic acidosis" (Ex. No. B–59 at 8). This means, conversely, that approximately 60% of the reported cases of lactic acidosis occurred at the recommended dosage of 100 milligrams or less.

There have been serveral documented suicide attempts where people have taken an overdose of phenformin and

[4] Although hypertension is not listed as a contraindication according to the January 1977 label restrictions, it may be associated with various degrees of cardiovascular disease. The label specifically lists "any acute medical situation such as cardiovascular collapse (shock), congestive heart failure [or] acute or suspected myocardial infarction" as contraindications. The label's failure to indicate whether hypertension is considered a cardiovascular disease further points out the difficulty physicians encounter when attempting to follow the label restrictions.

developed lactic acidosis as a direct result (Ex. No. B–479 at 11). Dr. Cohen, *et al.*, reported the case of a previously healthy 17 year old boy who took 1500–2000 mg at 6 p.m. and at 8:30 a.m. the next morning was admitted to the hospital suffering from lactic acidosis (Ex. No. B–63 at 43–44). The researchers concluded that "* * * the close relationship of the time of first administration of Phenformin to the onset of lactic acidosis together with the absence of arterial oxygen desaturation, hypotension, or peripheral vasoconstriction leaves little doubt that Phenformin was directly responsible for the lactic acidosis" (Ex. No. B–63 at 44).

In his testimony, Dr. Davidoff described a published report of a German woman who developed servere lactic acidosis while on phenformin. She was 57, had been taking a daily dosage of 150 mg and had the predisposing factors of cardiac failure an slight renal failure. When admitted to the clinic her lactate levels measures almost 19mEg/L (Ex. No. B–479 at 12–13). After the patient had recovered, she was placed back on phenformin under close supervision, with her blood tests being followed in order to establish whether or not phenformin had been a contributing factor in her lactic acidosis. Over a period of one week on 150 mg per day, her lactate which started at about one mEg/L rose to almost 4 mEg/L. Dr. Davidoff indicated that a rise is very unusual for patients taking phenformin. Therefore, phenformin was discontinued. This patient seemed to be biochemically at risk to excess accumulation of lactate. This case clearly indicate that phenformin was a contributing factor in lactic acidosis (Ex. No. B–479 at 13–14).

The analysis of phenformin dosage in 44 cases by Dr. Cohen, *et al.*, of the time intervals between the start of phenformin therapy, or an increase in dose, and the onset of lactic acidosis showed that 24 out of 34 patients in whom sufficient data was available developed lactic acidosis wihtin 2 months of the start of therapiutic doses. The onset of lactic acidosis occurred within two weeks in 17 patients (Ex. No. B–63 at 44). "If lactic acidosis had resulted purely from longstanding conditions such as cirrhosis or diabetes, such an early concentration of incidence would not have been expected" (Ex. No. B–63 at 44).

The UGDP study was a long-term prospective clinical trial carried out mainly in the sixties. It was designed to determine the effects of hypoglycemic agents on vascular complications in adult-onset diabetes and not to determine the incidence of lactic acidosis in phenformin users (Ex. No. B–396). There were 204 patients randomly assigned to phenformin (Ex. No. B–396 at 67). The daily phenformin dosage was 100 mg (Ex. No. B–396 at 65). In the phenformin-treated group one death was ascribed to lactic acidosis and two cases of nonfatal lactic acidosis were reported (Ex. No. B–396 at 72). The one patient who died of lactic acidosis had cardiovascular and renal disease along with hypertension (Tr. 536). Only renal disease with uremia was contraindicated in the labeling at the time phenformin was prescribed for her [Ex. No. B–506(e)]. No data was available with respect to the two nonfatal cases of lactic acidosis.

Gale and Tattersall conducted a retrospective study at General Hospital, Nottingham, from 1972–1975 and found eight diabetics with lactic acidosis that met their criteria of a blood lactate concentration of over 7 mmol/1 or an anion gap greater than 30 mmol/1 with a negative Acetest reaction on undiluted plasma. All eight lactic acidosis patients were taking phenformin and all died (Ex. No. B–96 at 973). Five patients were taking only 100 mg per day (Ex. No. B–96 at 974). Two patients were contraindicated, four had hypertension and minial evidence of renal disease, and two had no predisposing factors (Ex. No. B–96 at 972). Of the two noncontraindicated patients, one was taking only 100 mg daily, while the dosage of the other one could not be determined from the record. Lactic acidosis developed rapidly with an increased dosage of 200 mg per day after 5 days in 1 patient and after 15 days in another. Still another developed lactic acidosis after only 5 days on 100 mg while 2 others on 100 mg got lactic acidosis within 6 months. The 3 patients on 100 mg developed lactic acidosis 2 to 8 years after starting phenformin.

The Wise and Chapman study found that during a two-year period 38 diabetics with lactic acidosis were admitted to the Royal Adelaide Hospital. The criteria for establishing lactic acidosis was a lactic value of 2 mmol/1 or more and an arterial pH of less than 7.37. Twenty of the 38 patients were on phenformin with 15 having nonketotic or metabolic lactic acidosis. Of these 15 patients, ten received a daily dosage of 100 mg or less alone or in combination with sulphonylureas or insulin. Duration of phenformin treatment ranged from less than a month for five cases, from one month to a year for three cases, and one to ten years for seven cases (Ex. No. B–272 at 70). Seven patients had either started the drug or received a dose increase within the month before the occurrence of lactic acidosis (Ex. No. B–272 at 72). Six of the ten patients receiving 100 mg or less died (Ex. No. B–272 at 71). All but one of the 15 patients had additional renal or cardiovascular abnormalities or both (Ex. No. B–272 at 70).

Dr. Palumbo of the Mayo Clinic stated that he had never personally "* * * seen lactic acidosis in diabetics not treated with phenformin" (Ex. No. B–503 at 10). Dr. Kreisberg testified that:

> It is striking and almost an invariable finding that lactic acidosis in diabetics in our emergency room, in the absence of myocardial infarction and all other things that are known to produce lactic acidosis, is seen within the framework of the use of phenformin (Ex. No. B–499 at 18).

Dr. John Davidson, who sees two or three cases per year of phenformin-associated lactic acidosis at Grady Memorial Hospital in Atlanta, testified that he didn't remember having seen a diabetic with lactic acidosis in the last few years who was not on phenformin therapy (Ex. No. B–485 at 12).

Through the Diabetes Literature Index, Dr. Davidoff totaled the recorded cases of lactic acidosis and said:

> * * * without trying to be exhaustive, I was able to come up, I think in 1975, with something of the order of 104 cases of what appeared to be phenformin-associated lactic acidosis out of about 163 total cases of lactic acidosis in the literature and noted that there had been more since that effort on my part to actually add up the numbers (Ex. No. B–479 at 10).

Dr. Daughaday, who has been alert to the problems of lactic acidosis for at least 15 years, sees 1 to 3 cases of phenformin-associated lactic acidosis a year (Ex. No. B–473 at 11), while Dr. Felts for the last ten years has consulted on one or two cases per year of phenformin-associated lactic acidosis (Ex. No. B–477 at 5–6). Dr. Loewenstein of LSU School of Medicine said that "At our institution, most of the diabetics who have had lactic acidosis, in fact, almost all of the diabetics have been taking phenformin" (Tr. 47). Finally, Dr. Felig of Yale said:

> It should be emphasized that where lactic acidosis has been seen in diabetic patients within the last 10 years, it has been virtually always in association with phenformin administration (Tr. 276).

In all probability the cases in evidence are only a portion of those occurring in the United States. While underestimation will not establish an accurate rate for the incidence of phenformin-associated lactic acidosis, the cases are nevertheless valuable for

establishing an association. Dr. Wright published a report in July 1977 of four cases of phenformin-associated lactic acidosis in a three-week period at an Alabama hospital (Ex. No. B–510). This evidences that these cases are appearing more frequently than formerly believed.

These studies which are the best available in the record strongly establish an association between phenformin and lactic acidosis. When the sum total of these phenformin-treated lactic acidosis case studies are reviewed, along with the specific cases of lactic acidosis occurring during phenformin therapy which conform to the January 1977 label restrictions, there can be no doubt that an association exists between phenformin and lactic acidosis.

Ciba-Geigy's Evidence

Ciba-Geigy's evidence concerning the American Diabetic patient population's risk of lactic acidosis related to phenformin therapy consists largely of the Ciba-Geigy study conducted by Dr. Henry, which is comprised of two types of information. One type consists of cases reported in the literature and/or directly reported to the company, while the other is made up of the testimony of diabetologists which shows that within the group of patients under their care, there is virtually no incidence of lactic acidosis associated with phenformin therapy. The Ciba-Geigy study appears to suffer from several defects. Dr. Henry depends on the cases reported in the literature as part of his evaluation of the lactic acidosis rate associated with phenformin use but does not make any adjustments for the usual decrease in the number of articles published on any subject once the medical community has started to lose interest in it.

Professional journals have published studies and commentaries concerning the association of phenformin and lactic acidosis for several years. This has resulted in a large number of cases being reported within a limited time period. Once a controversy is considered resolved, the medical community is likely to lose interest in it as a subject for research efforts or for articles reporting occurrences of a suspected effect. This lagging interest normally results in fewer papers being submitted and accepted for publication in areas deemed sufficiently investigated and well understood by the medical community.

In substantiation of the theory that the reporting of the side effects of phenformin is following this trend, testimony was given which suggests that the recent decease of reporting in the literature of phenformin-associated lactic acidosis is due to the aforementioned factors rather than a shift in the lactic acidosis incidence levels in the percentage of the diabetic population for which phenformin is prescribed. Dr. Bressler, an editor of the American Journal of Medical Science, testified that:

> We would not even consider printing any more association between phenformin and lactic acidosis because it is such "old hat" now that it is no longer news. Everyone knows it, and I think that now the literature is vastly underreporting something that is well-known (Ex. No. B–475 at 12).

The reliability of the other aspect of the Ciba-Geigy estimation of the rate of occurrence of phenformin-associated lactic acidosis in the American public is also questionable. It is based on cases culled from voluntary reporting to the manufacturers by physicians which can be inaccurate since the method often results in an incomplete polling of the actual number of cases. The foreign polling experience is very useful in estimating the comparative reliability and accuracy of techniques used to gather data on phenformin-associated lactic acidosis. In making estimates of the effects of a drug on the total population in foreign countries, dependence on voluntary reporting systems rather than on systematic hospital record searches have considerably reduced the accuracy of surveys. Dr. Brown testified that the reporting from individual hospital studies uncovered four to forty times the percentage of cases that were detectable by the voluntary reporting method (Ex. No. B–481 at 8). Use of foreign data for this limited purpose is unrelated to the question of relying on foreign data in determining the safety of a drug.

There appears to be a proportional difference in the results obtained by direct polling and voluntary reporting within a country. This proportion is similar to that obtained when comparing the results of direct polling from other countries with the Ciba-Geigy estimates based on voluntary reporting (Ex. No. B–481 at 8–9). This parallel further supports an analogy of the foreign to the domestic polling procedure, and gives credibility to the domestic findings of an association between phenformin therapy and the incidence of lactic acidosis.

The fact that a disparity exists between voluntarily reported cases and actual occurrences in the United States was demonstrated by the testimony of Dr. Loewenstein. When asked on cross-examination why he reported cases to the FDA and not to Ciba-Geigy, he replied that:

> I felt that my obligation was to report to the Food and Drug Administration. I did not feel any obligation to report to the manufacturers who had overlooked lactic acidosis for a number of years (Tr. 43).

While it is unknown how widespread this sentiment is in the medical community, such a consideration, when viewed in light of the foreign polling experience, suggests that the process used by Ciba-Geigy to determine the frequency of the phenformin-associated lactic acidosis in the American population cannot be considered to result in a complete census.

By the testimony of a Ciba-Geigy witness, underreporting to drug companies may be alleviated by attention being drawn to a subject (Tr. 505). It is not illogical to assume, therefore, that when a controversy has been resolved in the minds of the medical community, the rate of reporting would decline. As stated by Dr. Brown, "There are serious fluctuations in the reporting depending on publicity, medical publication and other things happening in the medical world" (Ex. No. B–481 at 29). Such fluctuations appear to have occurred in the present case, raising serious questions as to the reliability of this aspect of the Ciba-Geigy study.

Reporting to companies has been characterized by Dr. Stolley, an epidemiologist, as "the basement estimate" of an occurrence rate (Tr. 339). Echoing this view, Dr. Davidoff testified that, due to the limitation of voluntary reporting systems, the cases discovered by Ciba-Geigy constitute only "the tip of the iceberg" of the total number of cases (Ex. No. B–429 at 11). Another deficiency in the Ciba-Geigy study lies in the standards, devised by Dr. Henry, for excluding cases from consideration. Since Dr. Henry is not a diabetologist, an epidemiologist, or a statistician, his background does not appear to qualify him as an expert with the training and experience necessary to make such determinations (Tr. 624).

It is unclear how the standard required of a lactate level of 6.5 mEq/L or greater with a pH of 7.33 or less was arrived at, especially as one authority is quoted by Dr. Henry as finding any lactate level of 1.3 mEq/L or above at a pH of 7.3 or less as diagnostic of lactic acidosis (Ex. No. CG–26 at 3). Interestingly, there is evidence in the record indicating that blood levels of lactate from 7–8 mEq/L are virtually always fatal (Ex. No. B–184).

Dr. Henry excluded from consideration in his study data and literature which "lacks information necessary to confirm the reported diagnosis of lactic acidosis." It is not clear whether this information was requested from the submitting physician to supplement reports deemed inadequate by Dr. Henry or if the submitted reports were rejected summarily when they did not contain this information. If the published literature or submitted reports were unaccompanied by data that Ciba-Geigy considered necessary for the confirmation of the diagnosis, they may not have been included in the study. Such an exclusion technique in polling, however, does not assure that the data did not exist, but only that it was not submitted in particularity to Ciba-Geigy under the voluntary reporting system or was not included in the article reported in the literature. Eliminating these cases from consideration in the study could considerably distort the final results (Ex. No. CG–26 at 2).

Dr. Henry's lack of expertise raises additional questions concerning the amount of reliance this study merits. Of 234 cases submitted which passed the severe "confirmed lactic acidosis" requirement, 195 were rejected as having "casual, predisposing, or contributory conditions or factors." The decision to eliminate these cases from the study was presumably made by Dr. Henry, since there is no evidence to the contrary.

Ciba-Geigy has used the entire group of patients receiving phenformin therapy in the United States to calculate the base population to which the affected cases will be compared in determining the percentage of users likely to suffer lactic acidosis associated with phenformin treatment. For this reason, the accuracy of Ciba-Geigy's determination depends on the completeness of the polling procedure.

Considering the methods of information collection utilized in this study and the questionable standards employed in evaluating those cases which were considered, the Ciba-Geigy study cannot qualify as a reasonable determination of the total number of phenformin-associated lactic acidosis cases occurring in the United States. A fair view of this study demonstrates it to be flawed to such an extent as to preclude its being afforded any significant evidentiary weight, particularly in view of the results of many other studies which demonstrate considerably higher levels of phenformin-associated lactic acidosis.

The second line of epidemiological proof of the safety of phenformin offered by Ciba-Geigy involves the administration of phenformin by diabetologists. These diabetologists demonstrated extraordinary success in using phenformin without incurring the lactic acidosis side effect. Many indicate that in years of using this drug, they have never seen a case of phenformin-associated lactic acidosis in patients under their care (Ex. Nos. CG–2 at 2, CG–4 at 4, CG–6 at 1, CG–7 at 3, CG–9 at 2, CG–12 at 6, CG–11 at 3, C–14 at 1, CG–15 at 1, CG–16 at 2, CG–22 at 3, CG–51 at 2, Tr. 425 and Tr. 524). When cases of phenformin-associated lactic acidosis were observed, they were attributed to patient overdosage (Ex. Nos. CG–5 at 3 and CG–18 at 3), patient ingestion of alcohol (Ex. Nos. CG–17 at 3, CG–20 at 3), or in the case of one patient, simply mentioned as an observed case of lactic acidosis (Ex. No. CG–10 at 3). Considering the large number of patients treated by these diabetologists without any incidence of lactic acidosis, the rate of occurrence in this population is extremely small.

While at first blush, this testimony may appear to substantiate the safety of phenformin, expert testimony from both parties distinguishes between the incidence of lactic acidosis when phenformin is administered by a diabetologist and when it is administered by a generalist (Ex. Nos. B–477 at 5, B–493 at 4, CG–2 at 4, CG–12 at 9 and Tr. 116). This particular group of patients had the benefit of being treasted by diabetologists rather than by primary physicians. Additionally, these diabetologists are characterized by the manufacturers as the most eminent in the United States (Ciba-Geigy USV Brief at 32–33). The results of the experience of such extraordinarily qualified doctors may be inappropriate for extrapolation to the treatment by other experts (Tr. 118).

When comparing such a minute incidence of phenformin-associated lactice acidosis in these expert-treated patients to the nationwide occurrence rate, it appears that the cases in the United State must be occurring in that portion of the diabetic population cared for by generalists (Ex. No. CG–10 at 3). This phenomenon has been observed in the case of chloramphenicol and other drugs (Tr. 383 and 347).

While many of the Ciba-Geigy diabetologist witnesses have never seen a case of lactic acidosis among their phenformin patients, several of them have consulted on cases of phenformin-associated lactic acidosis and have suggested these occurrences may be caused by inexperienced doctors or improper diagnosis of predisposing disease and lack of follow-up (Ex. No. CG–14, at 2 and Tr. 425). Ciba-Geigy witness Dr. Bowers noted that the incidence of lactic acidosis varies inversely with the percentage of experienced practitioners in a hospital. She testified that "A teaching hospital where inexperienced physicians abound might well have a much higher incidence [of phenformin-associated lactic acidosis]" (Ex. No. CG–2 at 4). Ciba-Geigy witness Dr. Mirskey testified that phenformin has not proven to be a dangerous drug in the hands of a diabetologist with extensive experience in the treatment of diabetes (Ex. No. CG–12 at 9).

Ciba-Geigy and USV assert that: The Bureau's argument, based on the views of research-oriented physicians such as Dr. Felig, seems to rest on the premise that while phenformin may arguably be safe in the hands of recognized experts, the ordinary practicing physician cannot be entrusted with it. This elitist approach demeans the medical profession and has no basis in the record other than as unsupported speculation. (Ciba-Geigy-USV Brief at 18).

Ciba-Geigy's accusation appears misplaced in view of the testimony of Ciba-Geigy witnesses discussed above and the disparity in the number of phenformin-associated lactic acidosis cases observed in the practices of specialists as compared to that seen in the total patient population. If an effect is observed in only one portion of a population, with the rest in this group remaining relatively free of the effect, then the estimated rate for the entire population would constitute and underestimation for the affected portion of the group. the absence of phenformin-associated lactic acidosis in patients under the care of specialist makes the positive results reported by the Bureau's witnesses of even more significance in a total population determination. As the affected group is considered on a total, undifferentiated population basis, their estimated risk is diluted by the inclusion of the above-mentioned no-risk group. There is the likelihood, therefore, of a patient population which is running a considerable risk of phenformin-associated lactic acidosis.

Ciba-Geigy and USV assert that the FDA does not " * * * have any statutory authority for differentiating between classes of physicians as to the drugs which may be prescribed (Ciba-Geigy-USV Brief at 18). Nevertheless, proof of the safety of phenformin when administered by specialists is insufficient to justify continued approval of phenformin because the majority of

diabetics are treated by their primary physician rather than specialists (Tr. 116–117). If phenformin is to enjoy continued marketing, it will be available to all physicians without regard to their expertise or experience. If doctors are unable to prescribe phenformin without endangering the lives of their patients, the low risk of danger of this drug when in the hands of an expert does not *a priori* justify its continued marketing. The FDA is, as stated by Ciba-Geigy-USV, powerless to limit approval of a drug only to administration by specialists. Therefore, if phenformin is unsafe when administered by generalists because its risk to the American public at large is greater than its benefit, its approval must be withdrawn.

Detection of Predisposing Factors

Ciba-Geigy and USV suggest that the adverse effects of phenformin therapy occur only when patients have some deficiency which predisposes them to lactic acidosis. They view these adverse effects as avoidable by testing the patient for these factors prior to the administration of the drug (Ciba-Geigy-USV Brief at 55). To substantiate this argument, it must be shown that the preexisting condition would have been diagnosed at the time the drug was prescribed using methods that are likely to be part of the usual practice of the medical community. Furthermore, it must be shown that any development of these predisposing factors after treatment would be identified and would result in the withdrawal of the medication before the onset of lactic acidosis.

Dr. Beaser testified that the lactic acidosis induced by predisposing factors can be guarded against by testing:

> * * * that any doctor, and I say doctor, not just internist, would be expected to do in a patient in present day medicine, who is being seen as a continually observed patient (Tr. 522).

Dr. Leibel concurs in this view (Ex. No. CG–51 at 3). Dr. Levine holds a similar opinion, noting that this battery of tests has kept his patients free from the lactic acidosis side effect of phenformin therapy (Tr. 428). Dr. Schoenberger also suggests the usefulness of such a screening, limiting his renal function testing to specific gravity and serum creatinine or blood urea nitrogen (Tr. 489). He resorts to the creatinine clearance test only when the previous tests indicate renal dysfunction (Tr. 502).

On the other hand, the Bureau's witnesses feel that creatinine clearance testing, which is considered a sophisticated test (Ex. No. B–495 at 4), is necessary to avoid many of the problems associated with phenformin treatment because the serum creatinine test is insufficient to exclude the possibility of preexisting renal dysfunction (Ex. Nos. B–503 at 12, B–495 at 4 and Tr. 115). Serum creatinine level can increase by 100% and still be within normal limits as established for this test. Furthermore, there can be a full 50% loss of kidney mass before a serum creatinine test will reveal kidney malfunction (Ex. No. B–483 at 9). There are specific cases where the serum creatinine test did not reveal renal dysfunction that was detected by the creatinine clearance test (Ex. No. B–489 at 13). Only the creatinine clearance test can detect the early stage of renal insufficiency (Ex. No. B–503 at 13).

Ciba-Geigy and its witnesses have extolled the use of phenformin in elderly patients (Ex. Nos. CG–5 at 3, CG–6, CG Brief at 41). In fact, one study has shown that they make up a majority of the population receiving this drug (Ex. No. B–493 at 1). However, it appears that the serum creatinine test is particularly inaccurate in this group of patients (Ex. Nos. B–483 at 10, B–489 at 11).

As a possibility of lactic acidosis is involved, full renal function is particularly vital as the rate of excretion of acid falls by half when phenformin is administered at dosages at or below that recommended by the package inserts (Ex. No. B–471 at 11). Renal insufficiency appears to cause disruption of protein-bound drugs, one of which is phenformin, causing a release of more free biologically active drugs (Ex. Nos. B–483 at 5 and 20). It is important to note the fact that the creatinine clearance test is sophisticated enough (Ex. No. B–495 at 4) that it will not be done by the primary physicians (Ex. No. B–483 at 10, Tr. 116) who constitute the main source of care for the diabetic patient (Tr. 116).

Ciba-Geigy witness Dr. Beaser, a diabetologist, does not do a creatinine clearance test in his screening of potential phenformin patients (Tr. 592) and knows of no one else who screens with this test (Tr. 594). He testified that the test is mainly a research tool which is very rarely utilized even in teaching hospitals despite the fact that it is a more sensitive test of renal dysfunction than the serum creatinine test (Tr. 593). This was experienced by another witness who had difficulty convincing experts to perform this test in candidates for phenformin therapy (Ex. No. B–473 at 8). Since the current labeling lists as a contraindication for phenformin therapy "renal disease with even mild degrees of impaired renal function" (Ex. No. B–506(n)), it appears that compliance with the label requirements at the primary physician level or with consistency in the practice of specialists is unlikely to prevent the occurrence of lactic acidosis (Ex. No. B–473). This situation is not an aspersion on the abilities of these physicians but rather the practical reality of the present circumstances of the practice of American medicine.

Acute or chronic liver disease is another contraindication of phenformin therapy. As with the kidney situation, time and cost considerations cause primary physicians to do a less than thorough workup for liver disease prior to prescribing phenformin (Tr. 121). Even when tests appear to demonstrate normal hepatic function, there still exists the possibility of liver disease, since the most common test reflects only acute cell damage (Tr. 119). Therefore, severe but chronic liver damage is likely to remain undetected. Proper liver function is particularly important in that phenformin appears to impair the removal of lactate from the blood by the liver (Tr. 29).

Even if phenformin was not primarily causal of lactic acidosis, if it impairs the body's ability to deal with stress situations (Ex. No. B–501 at 5) by displaying heightened biological activity, impairing excretion of acid, slowing metabolism of lactic acid and/or increasing production of lactic acid, it remains an insidious drug with dangerous repercussions for its users. Inability to control a spontaneous acidotic situation that would normally be compensated for by the body may be just as dangerous, if not more so, than having lactic acidosis initially instigated by a drug.

Assuming that physicians can and do properly administer phenformin in accordance with the January 1977 label requirements, there is still evidence that lactic acidosis occurs in noncontraindicated patients receiving the recommended dosage of 100 milligrams or less. Dr. Fulop reported four cases of lactic acidosis in diabetics taking phenformin at daily doses of not more than 100 milligrams who had no serious associated diseases (Ex. No. B–493 at 13). The Gale and Tattersall retrospective study reported one case of fatal lactic acidosis for a patient taking only 100 milligrams per day. There was no clinical or necropsy evidence of predisposing causes other than the drug (Ex. No. B–96 at 975).

Ciba-Geigy's review of reported lactic acidosis cases found 39 cases of phenformin-treated patients with

confirmed lactic acidosis for which no known causal, predisposing or contributory conditions or factors could be identified (Ex. No. B–59 at 5). Seventeen of those 39 patients were on daily dosages of 100 milligrams or less. In fact, 46.9% of the total 39 were on the recommended 100 milligrams per day (Ex. No. B–59, Table 4, at 15). The record does not indicate whether Dr. Fulop reported his four cases to Ciba-Geigy so there is a possibility that his cases may have been cited twice.

There are also examples of lactic acidosis developing with daily dosages of the recommended 100 milligrams or less for which the presence or absence of contraindications could not be determined from the record. Dr. Tranquada reported four cases of lactic acidosis whose daily doses were 50, 75, 100, and 100 milligrams respectively (Ex. No. B–467 at 11), while Dr. Loewenstein presented two cases of lactic acidosis with a daily dosage of 100 milligrams and two cases of lactic acidosis with a daily dose of 50 milligrams (Ex. No. B–471 at 31).

Analyzing the dosages being taken at the time of the onset of lactic acidosis, Dr. Woods and Dr. Cohen reviewed 44 cases and found 25 patients taking 100 milligrams or less daily. Of the 25, 18 were taking daily dosages of 100 milligrams, four were taking 75 milligrams, and three were taking 50 milligrams. Information concerning contraindications was not available from the record (Ex. No. B–412 at 180).

There are other examples of phenformin-associated lactic acidosis in noncontraindicated patients for which information on dosages was not indicated or could not be determined from the record. Using the January 1977 label contraindications, Dr. Loewenstein reported eight cases of phenformin-associated lactic acidosis for which only two of the eight patients were contraindicated (Ex. No. B–471 at 30). In his own personal experience, Dr. Tranquada had nine patients receiving between 50 and 200 milligrams per day who developed lactic acidosis and none of them had any other identifiable cause of lactic acidosis. One patient was a 23-year old woman who was in good health except for diabetes. She had not received any other therapy and had no recognizable cause of lactic acidosis other than phenformin (Ex. No. B–467 at 8).

Eight of the nine patients had impaired renal function at the time lactic acidosis was diagnosed but " * * * [e]vidence of renal dysfunction is a common accompaniment of lactic acidosis" (ex. No. B–467 at 12). Dr. Tranquada could not tell whether the impaired renal function was related to lactic acidosis or was a preexisting condition (Ex. No. B–467 at 12). Dr. Beaser testified that unless he had some pre-illness information, he could not determine if a patient's renal problems were caused by the lactic acidosis. The three patients who survived lactic acidosis had normal renal function after recovery (Ex. No. B–467 at 13). This indicates that the impaired renal function was due to the lactic acidosis.

Dr. Davidoff reported three cases of lactic acidosis in 1970 and four cases of lactic acidosis in 1971 with no obvious precipitating causes. All seven patients were taking phenformin but information about dosages was not available in the record (Ex. No. B–479 at 5). The Gale and Tattersall study also identified another case of phenformin-associated lactic acidosis for which there were no predisposing factors. Dosage could not be determined from the study (Ex. No. B–98 at 974).

Inability to Comply With Label Requirements

Ciba-Geigy and USV assert that phenformin's effects should be considered only with regard to those patients who fall within the present label requirements (Ciba-Geigy-USV Brief at 20). The statute talks in terms of an evaluation of a drug under the conditions of use prescribed, recommended, or suggested in the labeling.

Congress did not intend that the FDA should substitute its judgment for that of the individual physician. Nor did it intend a finding of lack of safety to be supported by the fact that a particular drug may be misused or prescribed contrary to the approved labeling. Physicians are continually faced with making decisions based on their individual medical judgment in light of the overall circumstances and conditions relating to the individual patient for whom medication is being prescribed.

Therefore, where the statute deals with safety, it talks in terms of findings for particular medications under the conditions of use "prescribed, recommended, or suggested in the proposed labeling" and not under the actual condition of use. This is not to say that where the suggested conditions of use are so vague or unreasonably restrictive as to preclude reasonable expectation of their being complied with, the drug must nevertheless be found shown to be safe on the basis of results obtained when administered to an unrealistically limited patient population.

The fact, as indicated by the record, that the label restrictions for phenformin may not be strictly complied with, does not constitute the only source of danger associated with the use of phenformin. The principal difficulty is that the general practitioners who care for the majority of adult-onset diabetics would be unable in their normal practice to discover the existence of all predisposing factors of lactic acidosis and would therefore be unable to comply with the conditions of use prescribed, recommended or suggested in the labeling.

Doctors who treat their patients in apparent good faith compliance with the package requirements for phenformin will nevertheless be unable to avoid the possibility of a lactic acidosis side effect. Available tests are generally unable to rule out renal and hepatic insufficiency. Furthermore, lactic acidosis may occur within as little as two to three weeks after beginning phenformin therapy (Ex. No. B–471 at 19 and Ex. No. B–63 at 44). Such short periods could obviously occur between visits to a physician. These facts require the conclusion that label restriction of patients for whom phenformin is contraindicated cannot reasonably be expected to result in the desired limitation of the population to which it will be administered. The actual population receiving phenformin would therefore be considered more at risk for lactic acidosis than the population envisioned by the manufacturers and sought to be provided by the labeling.

Consideration of the adverse effects in the actual population receiving phenformin is appropriate to a determination of its safety. The absence of similarly adverse effects in the more limited patient population, as recommended by the labeling, would be misleading unless it is demonstrated that the recommended labeling can reasonably be expected to limit the actual patient population receiving the drug. As indicated, phenformin labeling cannot reasonably be expected to do this.

Although the prescription of a drug outside of its package recommendation would not, *per se*, be considered as *prima facie* evidence as to its lack of safety for the purpose of withdrawal of approval of an NDA, the widespread use of a drug contrary to the label requirements should not be ignored. This is particularly true when the prescription practices outside of label requirements are widespread,

predictable and substantiated by epidemiological trends in evidence.

Ciba-Geigy and USV decry any attempt of the Bureau to "take away from the prescribing physicians the very latitude and discretion the Food , Drug and Cosmetic Act was specifically structured to protect" (CG–USV Brief at 59–60), apparently agreeing with an interpretation of the Act that:

> Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration [37 FR 16503 (1972)].

The majority of lactic acidosis cases associated with phenformin therapy reported to Ciba-Geigy were eliminated from consideration in the Ciba-Geigy study on the basis that the administration of the drug was not within the confines of the label requirements. It therefore appears that there are many cases of the American medical community not complying with the label requirements when prescribing phenformin.

In reporting on a study designed to ascertain the rate of physician compliance with label warnings, Dr Stolley arrived at several important conclusions. First, it was found that drugs continued to be prescribed contrary to label warnings even though they were dangerous drugs whose use should be limited. Chloramphenicol enjoyed a very widespread general use despite its very restrictive label warnings (Tr. 347). As to the results of interviews with various doctors, Dr. Stolley stated that:

> We found that they were aware of this warning but in their own experience they had never seen the aplastic anemia associated with chloramphenicol because it is a somewhat rare adverse reaction. Therefore, they continued to use it (Tr. 348).

The research showed that doctors with isolated practice and little opportunity for exchange of information with colleagues were more apt to be among those prescribing the drug beyond the limits of the labeling. The situation in the chloramphenicol case appears comparable to the phenformin situation insofar as the profile of adverse side effects in chloramphenicol parallels the phenformin situation. Generalists who see only a small number of diabetics would be less likely to have observed the lactic acidosis side effect of phenformin firsthand. Therefore, those doctors having little contact with specialized colleagues would be more likely to have a higher ratio of patients using phenformin despite contraindictions than would diabetologists. This difference in the prescription habits of generalists and specialists has been seen in the case of other drugs as well (Tr. 383).

Dr. Loewenstein, a diabetologist, withdrew a pateint from phenformin therapy who was previously taking the drug. Two weeks before her admission to a clinic for lactic acidosis and her subsequent death, she was admitted to a semi-rural hospital for control of hypertension and her physician then resumed phenformin at 150 milligrams per day which she continued taking it after she left the hospital. She subsequently developed lactic acidosis symptoms. This case occurred between January 1, 1976 and April 30, 1977, showing the labeling in effect at that time did not result in its being restricted to the patient population for whom it was indicated (Tr. 53).

As a practical matter, phenformin labeling is not susceptible to a high degree of compliance and cannot be reasonably expected to be closely followed by physicians. Therefore, the present labeling does not afford sufficient protection against the occurrence of serious side effects, and phenformin cannot be considered as shown to be safe as required by the statute.

Risk-Benefit

Any determination of continued approval of a drug requires an evaluation of the benefits as compared with the risks, if any, which occur from its usage. Therefore, a risk-benefit evaluation is a necessary part of the present determination.

Phenformin has been deemed by Ciba-Geigy and USV to lower blood sugar through direct action of the drug and by contributing to weight loss. They see these effects as resulting in the mitigation of the longer term deleterious effects of this disease. Ciba-Geigy and USV assert that phenformin has advantages over insulin therapy and is a viable therapeutic alternative when attempts at weight loss through diet fail.

Ciba-Geigy and USV believe that, as the matter of the sustained efficacy of phenformin in lowering blood sugar was not addressed in the May 6, 1977 Notice of Opportunity for Hearing, this question is not in issue in the present proceeding (CG–USV Brief at 12). The notice in question is brief, alleging that "No patient population can be identified in whom the possible benefits of phenformin therapy outweigh the risk of lactic acidosis, a complication that is frequently fatal" (42 FR 23170). Because proceedings attempting to delineate a limited population and distribution system appropriate to alleviate questions raised about phenformin therapy were continuing contemporaneously with the prehearing and might have affected the scope of the present proceeding, it was determined, as indicated in the Notice of Hearing, that the issues would be identified and agreed upon by the parties at the prehearing conference (42 FR 40959).

Accordingly, the issues were formulated at the prehearing conference of August 30, 1977, and reiterated in a Notice to Parties issued by the Office of the Administrative Law Judge on August 31, 1977. Issue number one is set forth in that notice as follows:

> Whether and to what extent, the use of phenformin is beneficial in the treatment of diabetic patients for whom the drug is indicated under the conditions of use prescribed, recommended, or suggested in its labeling.

Since they actively participated in the formulation of the issues at said prehearing conference, the manufacturers had actual notice that efficacy would be a subject under consideration in this proceeding.

The Bureau asserts that phenformin does not display any sustained blood sugar lowering effects, and so cannot ameliorate the long-term effects of diabetes which develop gradually. Furthermore, the Bureau contends that lowered blood sugar, even if sustained, does not address the entire spectrum of the ill effects of lack of insulin, whereas increased insulin, whether through direct administration or weight loss, will have an advantageous effect on numerous aspects of metabolism over a prolonged period of time.

Several witnesses agree that a hypoglycemic agent without the capacity for a sustained effect would not mitigate the long-term effects of diabetes (Tr. 296, Tr. 171, Ex. No. B–475 at 9). Testimony has been given concerning the limited nature of the decreased blood sugar resulting from phenformin therapy so that in the void of the wider range of effects accomplished by insulin, the long-term effects of diabetes may still occur (Ex. Nos. B–497 at 4, B–489 at 29, B–475 at 9, and B–487 at 14). It has been suggested that the observed decrease is quite modest (Ex. No. B–495 at 8) and temporary (Ex. No. B–469 at 9, Tr. 301). The synergistic effect when the drug is combined with sulfonamides also appears to be small (Ex. No. B–469 at 31). In substantiation of these assertions,

a study using phenformin and placebos in treatment showed that the blood sugar changes in these groups were comparable (Tr. 167).

Secondary failure of phenformin in lowering blood sugar levels have been observed to occur at various times after instigation of the therapy. Dr. Felig found that the rate of secondary failure varied from six months to 18 months (Tr. 296). The depressive effect of phenformin on blood glucose levels has been observed to dissipate at about two years after initiation of therapy (Ex. No. B–475 at 9). Dr. Prout has seen secondary failure at 2–3 years after the initial use of this drug (Tr. 200), as have other practitioners (Ex. No. B–473 at 6). There is testimony to the effect that chronic administration of phenformin results in a return to normal blood sugar levels (Ex. No. B–489 at 26). The ability of phenformin to control blood sugar levels in the long-term has been considered unimpressive (Ex. No. B–499 at 5).

The Ciba-Geigy evidence on this subject is sparse, consisting of brief statements by two of its witnesses to the effect that some of the patients under their care have not experienced a secondary failure of phenformin during several years of treatment. Dr. Levine testified that he had controlled the blood glucose levels of some of his patients with phenformin therapy for 10–12 years (Tr. 426). When questioned, he clarified that the patients remained on a diet regimen throughout the therapy (Tr. 479) and were also maintained on a program of physical exercise (Tr. 483). The long-range "effectiveness" of phenformin he observed may well be attributable to these concomitant therapies, especially as it has been shown that weight loss in such patients can decrease blood sugar levels and entirely alleviate diabetic symptoms. Therefore, Dr. Levine's expereince does not qualify as proof of the long-term effectiveness of phenformin therapy in lowering blood sugar levels.

Dr. Beaser has continued to use phenformin in some of his patients for as long as 15–18 years (Tr. 523). It is likely that his statement as to this long-term therapy is no more conclusive as to the extended efficacy of phenformin in lowering blood sugar than is Dr. Levine's, as diet concomitant with drug therapy is the average practice in this field. Further, a mere maintaining of a patient on a drug for a long period of time is no assurance of efficacy. There is evidence that most doctors will note changes in blood glucose levels only in the short term, and may not observe gradual increases in this level (Tr. 306–310). In any event, such weak, sketchy evidence of phenformin's long-term glucose-lowering effects, when compared to the other testimony and evidence on this matter, fails to demonstrate any long-term efficacy of this drug.

Another aspect of efficacy is the claim that phenformin acts to reduce the weight of a patient. The record indicates that this drug has little or no ability to reduce weight initially or to effect a long-term weight loss (Ex. Nos. B–497 at 4, B–475 at 13, and B–487 at 16). The minimal weight loss accomplished in association with phenformin therapy has been demonstrated to be transitory (Ex. No. B–501 at 11). One witness observed that no weight loss was demonstrated as a result of phenformin therapy in his practice (Ex. No. B–503 at 6). The UGDP Study indicates that phenformin does not result in weight loss (Ex. No. B–497 at 5), with both the phenformin-treated group and the placebo group losing 5% of their body weight (Tr. 164).

The two main alternative therapies to phenformin are weight loss through dietary regimen, which increases the output of natural insulin and increases the body's response to it, and the direct administration of insulin, which supplements the natural supply of insulin in the body. Weight loss has been determined to be the treatment of choice in adult onset diabetes by the unanimous consensus of the expert witnesses in this proceeding. The major difficulty encountered in this mode of therapy has been in effecting compliance with the diet regimen.

In one study, 90% of a patient population of 600 patients lost at least 20 pounds within two years of being removed from treatment by oral agents and placed on a diet (Ex. No. B–465 at 16). Another expert testified that effective diet regimens can be implemented, although compliance is always a difficulty encountered in diet therapy (Ex. No. B–473 at 5). Others have found diet control successful in a large percentage of their maturity onset diabetic patients (Ex. Nos. B–469 at 3 and B–503 at 4). Using a method coordinated with frequent follow-up and intensive education to mitigate compliance difficulties, one clinic accomplished an average weight loss of ten pounds per patient in the first week of the diet. This weight loss was accompanied by an abrupt lowering of blood sugar, resulting in an alleviation of symptoms and an increase in the patient motivation to follow the diet (Ex. No. B–465 at 5).

Insulin is another form of therapy which has been used as an alternative to phenformin therapy. Insulin is the therapeutic agent most effective in lowering blood sugar (Ex. Nos. B–479 at 17 and B–475 at 7). It does not appear to lead to vascular complication (Ex. No. B–473 at 5(a) and Tr. 293) and has advantages over phenformin therapy in that insulin decreases the development of the long-range complications of diabetes (Tr. 24) and regulates a range of metabolic functions rather than first blood sugar levels (Ex. No. B–487 at 12). Restricting a patient's choices of therapy to diet or insulin can encourage compliance with diet, which is the preferred treatment for maturity onset diabetes (Ex. No. B–503 at 4). Nonetheless, in one doctor's experience, when the advantages of insulin therapy were thorougly explained to the patients for whom diet proved unsuccessful, there was not a single refusal of insulin therapy (Tr. 8). Availability of phenformin therapy appears to discourage the use of insulin therapy (Tr. 104–105).

It appears from the record in this proceeding that phenformin therapy results in only minimal blood glucose lowering or weight loss effects. These effects are transient when compared with the many years over which the debilitating aspects of diabetes develop, limiting phenformin's ability to alleviate these problems. The alternative of weight loss through a diet regimen has been extolled by all the expert witnesses in this proceeding as the ideal method of treating adult onset diabetes. When diet has been rigorously pursued, a large portion of the patient population has responded with weight loss and normalization of blood sugar levels. Weight loss appears to increase the body's natural output of insulin as well as the tissues' sensitivity to it.

In cases where weight loss by diet is not accomplished or where the weight loss does not control the diabetes, direct insulin supplementation is often employed. Both diet and insulin therapy have the advantage of remaining effective during long-term therapy and affecting a range of metabolic functions rather than being limited in their effect to lowering blood glucose levels. Such a broad spectrum of activity is more likely to approximate normal metabolism and so circumvent the long-range debilitating effects of diabetes than is phenformin with its very short-term, limited influence. When considering that the side effect of phenformin therapy, lactic acidosis, gives rise to a mortality rate of from 50%–60% (Tr. 302, Ex. No. B–

493 at 8 and Tr. 298), its possible minimal benefit cannot outweigh its risk.

Patients for Whom Benefit of Phenformin Therapy May Outweigh Risks

Questions have been raised by Ciba-Geigy and USV concerning the loss of occupation of diabetic patients as a result of a change to insulin therapy. While insulin-dependent diabetics are prevented by statutory mandate from operating commercial vehicles in interstate or foreign commerce (49 CFR 391.41(b)(3)), diabetics who control their condition through diet and use of hypoglycemic agents do not come under this restriction.

An interstate operator of commercial vehicles obviously considers the ability to continue present employment as a benefit of phenformin therapy. However, the duration of such a benefit must be considered along with the risk in determining the issues in this proceeding. Phenformin's effectiveness has not been conclusively established, and studies submitted into evidence show that most people using phenformin must ultimately resort to insulin therapy for control of blood sugar. (See discussion of long-term efficacy in the Risk-Benefit Section of this decision).

Dr. Levine testified that 80% of sulfonylurea patients do not suffer secondary failure in the first year (Tr. 422). Thus, sulfonylurea drugs in most cases would give the diabetic sufficient time to make arrangements for job changes without subjecting him to the risk of lactic acidosis. Although a job change resulting from the development of diabetes would appear in the first instance a hardship, such a situation is analogous to an individual being forced to severely restrict or change his occupational options because of other health problems such as cardiovascular disorders or epilepsy. This difficulty is not entirely unique.

The purpose of 49 CFR 391.41(b)(3) is to protect the public. Insulin-dependent diabetics are subject to hypoglycemia which can be a direct cause of traffic accidents due to unconsciousness or errors in perception, attention or coordination. They may also be subject to hyperglycemia which results in progressive drowsiness, dizziness, headaches, and extreme weakness among other symptoms which generally have the same effect on driving tasks as hypoglycemia (42 FR 16456). Although diabetics on oral hypoglycemia agents may not be subject as often as insulin-dependent diabetics to hypoglycemia reactions (42 FR 16454), they still run the risk of these reactions. Thus, phenformin diabetics may also pose a similar risk to the public. The Federal Aviation Regulations make no distinction between insulin-dependent diabetics and diabetics controlled by oral hypoglycemia agents in prohibiting diabetics from receiving airline pilot licenses.

The question of limiting employment possibilities cannot preclude withdrawal of approval of phenformin. The needs of the small group for whom its temporary benefits may outweigh its risks cannot provide justification for its general marketing. To the extent administration of phenformin could actually be restricted to the limited patient population indicated by its current labeling, the risks of lactic acidosis would appear to be minimized. However, in view of the lack of proven long-term efficacy, continued approval would be questionable even without the problems associated with limiting the patient population.

It appears that the temporary benefits of phenformin could nevertheless be of therapeutic value in unusual cases such as where emotional or physical problems actually prevent administration of insulin. The small number of patients who are allergic to insulin or unresponsive to desenitization (Ex. No. B–465 at 13 and Tr. 199) and individuals whose livelihood depend on an orally-administered medication are possible candidates for such a limited distribution program. One such patient was a woman who had calcium deposits in her skin which precluded the administration of insulin and was allergic to sulfonylureas. The case was pointed out as being highly unusual in its nature (Ex. No. B–495 at 11).

On the other hand, inability of self-administration would apparently be an inadequate argument for special consideration because of the possibility of training family members or providing visiting nurses. In the case of the blind, premeasured syringes would be sufficient to allow self-administration of insulin. It appears, therefore, that the need may exist for a limited distribution of phenformin to special patients under specialized controlled treatment programs based on individual physician's informed medical judgment. However, such a program cannot be authorized within the parameters of this proceeding which is charged solely with determining the propriety of the proposed withdrawal of approval of the NDA's for general marketing of phenformin.[5]

[5] Along this line, it appears that some attempts are presently being made by FDA to provide for an extremely limited use of phenformin. On January 16, 1978, after briefs had been filed and the evidentiary record completed, Ciba-Geigy and USV jointly moved the admission of Ex. No. CG–81 into evidence. Exhibit No. CG–81 consists of a draft Federal Register notice designed to propose a limited distribution system, which as of this writing, has not been approved by the Commissioner. The motion is denied and Ex. No. CG–81 is not received into evidence because, as indicated, the implementation of a limited distribution system as contemplated in the prospective notice (Ex. No. CG–81) is outside the scope of this proceeding.

The manufacturers assert that "the most vital consideration is that phenformin, as currently labeled, is a uniquely beneficial therapy for a limited diabetic population" (Ciba-Geigy-USV Brief at 61). Such a stand would seem to be amenable to a carefully controlled distribution system that would make this medication available to such individuals without the problems of a concomitant risk to the majority of patients for whom phenformin therapy constitutes an inordinate risk, and for whom the label indication (for reasons previously stated) cannot reasonably be expected to provide sufficient protection.

CCD Witnesses

One additional matter requires consideration. CCD introduced written direct testimony which was in large measure directed to the question of the appropriateness of the Secretary's invoking of the imminent health hazard provision of § 505(e). However, this matter is not in issue in this proceeding which deals solely with the determination of whether the approval of the NDA's for phenformin should be withdrawn under § 505(e)(1), (2) and (3). To the extent the testimony of CCD witnesses did not deal with the Secretary's imminent hazard finding, it was generally repetitious of testimony given by these same witnesses on behalf of Ciba-Geigy.

Discussion and Conclusions

Although the phenomenon of phenformin-associated lactic acidosis is not totally understood, the compilation of the present data on the subject set forth in the evidentiary record of this proceeding allows some conclusions to be made concerning this association. The basic experimental research conducted to evaluate the effects of phenformin on the human body are revealing. Phenformin decreases the rate of absorption of glucose from the gut which accounts in part for the small hypoglycemic effect it displays. It also causes the body to shift from anaerobic to aerobic metabolism, causing increases in the blood lactate levels. Phenformin interferes with glyconeogenesis in the liver. This is the

liver's method of clearing the blood of excess lactate. These aspects of the action of phenformin result in the blockage of the body's important safety valves for lactic acid accumulation.

Increased lactate levels have been associated with increased phenformin levels in the blood. The manfacturers point to this tendency as allowing the safe use of phenformin by controlling the oral doses of this drug. The fact that lactic acidosis tends to occur at increased levels of phenformin is important since phenformin is eliminated from the body and/or is tied up in a bilogically inactive protein complex by normal liver and kidney function. Therfore, since substantial liver and kidney dysfunction can go undetected by the testing methods presently relied on by practicing physicians, keeping oral dosage within the parameters of the label requirements will not automatically restrict phenformin to safe levels in the bloodstream. Cases of phenformin-associated lactic acidosis have occurred even when the drug is administered within the parameters of the labeling requirements. Increased lactate levels and lactic acidosis have also been associated with normal blood levels of phenformin, demonstrating that individual sensitivity to the effects of phenformin may lead to lactic acidosis even if the blood level of this drug could be controlled.

The Bureau's evidence gives many examples of phenformin-associated lactic acidosis. While not all of the examples are as thoroughly documented as comparable animal studies, they provide valuable and extensive human epidemiologic evidence which shows an association between phenformin and lactic acidosis. Metabolic lactic acidosis appears to be an extemely rare occurrence among this patient population, and the fact that it occurs virtually exclusively among phenformin users is substantial proof that this association is valid. While no absolute quantification of the base rate of lactic acidosis for the diabetic population at large can be determined, this situation is typical of many diseases and does not detract from the demonstration of a strong association between phenformin and lactic acidosis.

The manufacturers' proof consists of the testimony of expert diabetologists and a Ciba-Geigy study. The experience of these diabetologists, while interesting, cannot be extrapolated to the realities of the practice of medicine at all levels, expecially as most diabetics are treated by their primary physicians. The Ciba-Geigy study suffers from many flaws. It relies on a voluntary reporting system which has historically uncovered only a small percentage of the cases which occur and on published cases which are subject to large fluctuations in rates of reporting. Furthermore, data which has been shown to be incomplete by the many other cases reported in the present proceeding was screened by questionable methods and extrapolated to the entire population receiving phenformin therapy. As a result, any deviation from a complete polling would result in a concomitant underestimation of the percentage of phenformin users who are lactic acidosis victims. Accordingly, the intrinsic unreliability of this study precludes its being given any significant weight.

A strong association between phenformin therapy conducted in good-faith compliance with the label requirements has been demonstrated. Further, it has been shown that label restrictions have not been strictly adhered to. The limited short-term benefits of this drug have not been shown to be justified in light of the risks attending its use. Under these circumstances, the prior approval of the NDA's for phenformin must be withdrawn. It appears that there may be some maturity onset diabetics with unusual physical or emotional difficulties for whom short-term administration of phenformin may, in the judgment of their physicians, be necessary despite the risk of lactic acidosis. Those individuals for whom this drug's benefits outweigh its risk may possibly be provided access to the drug despite its removal from general marketing through the experimental drug provisions or some other limited distribution system as previously mentioned. However, in lieu of such arrangements for limited distribution, the short-term beneficial effects of phenformin for a very small group cannot justify the risks associated with widespread marketing.

Ultimate Findings and Order

Consideration of the record in this proceeding requires the following ultimate findings:

1. Phenformin has limited short-term beneficial effect in the treatment of diabetics under the conditions of use prescribed, recommended or suggested in its labeling.

2. The conditions of use prescribed, recommended, or suggested in the labeling for phenformin are inadequate to exclude from treatment those persons for whom the drug is contraindicated as a result of factors which predispose patients to lactic acidosis.

3. The occurrence of lactic acidosis is associated with the use of phenformin in patients for whom the drug is indicated under its current labeling and the incidence of such occurrences as compared to the diabetic population at large is not susceptible of quantification on this record.

4. Therapeutic modalities other than phenformin are effective for treating patients for whom phenformin is indicated in its labeling without the same degree of risk associated with the use of phenformin.

5. The limited benefits of phenformin are insufficient to support a finding of safety in light of the risks attending its general marketing under the approved NDA's. Approval of the NDA's for phenformin should therefore be withdrawn pursuant to § 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e). Accordingly,

It is ordered, That the approval of the NDA's for phenformin, NDA 11-624, NDA 12-752, NDA 17-126 and NDA 17-127, and all supplemental NDA's be, and they are hereby, withdrawn pursuant to § 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e);

And it is further ordered, That in the absence of the timely filing of exceptions pursuant to § 12.125(a) (21 CFR 12.125(a)) or the issuance of a notice of review by the Commissioner pursuant to § 12.125(f) (21 CFR 12.125(f)), this initial decision shall become the final decision of the Commissioner pursuant to § 12.120(e) (21 CFR 12.120(e)) and shall be effective as of the date of publication of a notice to that effect in the **Federal Register** pursuant to § 12.120(f) (21 CFR 12.120(f)). Dated this 6th day of February 1978.

Daniel J. Davidson,
Administrative Law Judge.

Dated: March 30, 1979.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

[Docket No. 77N-0150]

[FR Doc. 79-10594 Filed 4-5-79; 8:45 am]

BILLING CODE 4110-03-M